Optimising the X-ray Visibility of Polyethylene Biomaterials (Alternative Format Thesis)

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Optimising the X-ray Visibility of Polyethylene Biomaterials

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Abstract

In the UK there are more than 200,000 joint replacements performed each year, and the majority of the implanted devices have an ultra-high molecular weight polyethylene bearing. Polyethylene has limited X-ray attenuation which means that on a standard radiograph the polyethylene bearing component of a joint replacement cannot be seen. Consequently, indirect methods have been developed to assess the condition of the polyethylene part based on the surrounding metallic component positioning; but these indirect methods cannot be used for devices designed without a metallic backing, and can cause misdiagnosis as a result of inaccuracies. In this thesis, a novel polyethylene with increased radiopacity has been created through the diffusion of an iodised oil-based contrast fluid (Lipiodol Ultra Fluid), and its suitability for the long-term medical application explored.

Prior to commencing the experiments, the key challenges in the development of a new polyethylene were identified through a literature review. The review revealed the radiopaque polyethylene was an original idea, but that the following criteria must be met; the temperature of the treatment needed to be carefully controlled to ensure material properties were maintained, the radiopacity needed to be sufficient to be clinically useful, the polyethylene needed to be manufacturable and commercially viable, and any degradation of the material *in vivo* needed to be minimised.

The influence of Lipiodol treatment on the tensile, physical and chemical properties of the polymer was investigated using infrared spectroscopy, differential scanning calorimetry and tensile testing. The optimal treatment condition of 105°C was identified from this experimental work, as polyethylene samples treated at this temperature had a significantly higher radiopacity (approximately 600 HU) and had tensile properties comparable with untreated polyethylene.

Once the treatment conditions had been chosen, the X-ray visibility of the radiopaque polyethylene under a clinical set-up was examined. The feasibility of using radiopaque polyethylene for model-based Roentgen Stereophotogrammetric Analysis (RSA) was investigated, and the precision and accuracy of the results reported for rotational or translational movements. The radiopaque polyethylene was found to have an X-ray attenuation sufficiently high to be visualised in standard radiographs, and it was possible to perform model-based RSA with a precision less than 0.06 mm for translational movements and more than 95% accuracy. The quality of the surface models was the main source of error, and this resulted from the radiopaque treatment causing swelling of the samples.

To better understand the parameters of the diffusion of the iodised oil into polyethylene, a practical finite-element model was developed for the prediction of the diffusion profile of Lipiodol into polyethylene. The model applied Fickian diffusion theory in three-dimensions and was able to accurately predict the diffusion profile within the polyethylene to within 80% accuracy. It was concluded that the diffusion behaviour of oil within polyethylene is not truly Fickian, as the experiments indicated that the diffusion coefficient of the semi-crystalline polymer varied with temperature. Nevertheless, the model was sufficiently accurate for use as a design aid for manufacturing planning of radiopaque polyethylene parts.

The final study investigated the influence of Lipiodol treatment on the chemical stability of polyethylene and quantified; oxidation after accelerated ageing, changes to mechanical properties after ageing, and leaching of the oil from of polyethylene under physiological conditions. Oil infused samples (with both Lipiodol and Vitamin E) showed higher tensile yield, ultimate strength, elongation at failure and oxidative stability compared with untreated polyethylene. Leaching of the Lipiodol did occur but stabilised after 2 weeks. The accelerated ageing reduced the radiopacity, and after 4 weeks the radiopacity had reduced by 54%, but the radiopaque polyethylene was still clearly visible on CT scans.

This research has examined the influence that the infusion of an oil-based contrast agent has on the properties of ultra-high molecular weight polyethylene. The feasibility of the material for clinical application for radiography-based techniques such as RSA, has been demonstrated, and accelerated ageing results indicate the chemical stability of the material is comparative to Vitamin E polyethylene.

Acknowledgements

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As they say, it takes a village to get a PhD and I would like to thank everyone in the Department of Mechanical Engineering, Claire, Vimal, Steve, Hamide, Nigel, Cheryl, James.... Without their support this work would have been impossible. I would also like to thank my assessors Prof Chris Bowen and Prof Cathy Holt for the tough but insightful viva.

Last but no least my amazing family (Maman, Baba and Parsa). Even though I had many doubters, you believed in me. Thank you for encouraging me to work toward my dreams. There is no word in any language to describe how much I am grateful for the everything that you have done for me. I love three of you a lot and I would like to dedicate this work to you.

Contents

Chapter 1

Introduction

1.1 Context and background

More than 60 years ago Charnley used high-density polyethylene in his low friction hip replacement design[1] and since then ultra-high molecular weight polyethylene (UHMWPE) has been the bearing material of choice for the majority of orthopaedic replacements. Other uses of polyethylene for medical applications include; replacement of ligaments, maxillofacial reconstruction implants, surgical sutures and meshes[1,3,2], and more recently it has been used as an alternative to metal wires when treating bone fractures[1].

According to the National Joint Registry[5] from April 2003 to December 2018, there were over 2.7 million joint replacements in the UK and in the majority of the cases polyethylene played an important role (as a bearing material between metallic parts, an all-polyethylene tibial component, or a polyethylene monobloc hip implant). Over the past ten years there has also been more interest in highly-crosslinked polyethylene implants[5], which have shown improved wear properties. Despite the suitability of UHMWPE for long–term medical applications, polyethylene materials can still wear, oxidise, dislocate or fracture, leading to patient discomfort and costly revision surgeries[6,7,8]. Early identification of failure can reduce patient discomfort, and reduce the risk of complications occurring prior to the revision surgery. However, due to the limited X-ray visibility of polyethylene, an early diagnosis of failure can be difficult and often requires expensive medical imaging equipment such as Magnetic Resonance Imaging (MRI). Moreover, the low X-ray attenuation of polyethylene means that any post-operative follow-up of polyethylene components has to be performed indirectly from information on any surrounding metallic components which can introduce error and is not always possible.

The clinical potential for a radiopaque polyethylene can be seen from case studies reported in the literature. A series of case studies reported by Huang *et al.* highlighted the poor clinical performance of the low–contact stress (LCS) knee replacement design[9]. One of those cases was a 78 year old female who 5 years after the surgery had a sudden subluxation of the

knee. Revision surgery revealed a fracture in the lateral meniscal bearing, and severe wear of the patellar bearing. The revised implant bearing also fractured three years later and it was found to relate to rotation of the metallic tibial tray; however, due to the age of the patient the surgeon decided not to revise the metallic components and just replace the broken bearing. Due to the low X-ray visibility of polyethylene part, the early diagnosis of failure was not possible from the standard radiograph. If the bearing had been visible it may have been possible to identify the significant wear of the bearing at an early stage, prompting the surgeon to perform a bearing exchange and preventing the later subluxation of the knee and the requirement for extensive revision surgery. Furthermore, such diagnoses could have highlighted the poor wear performance of the knee design early on in a clinical trial and prevent its widespread use.

A more recent example is a case study reported by Jeong *et al.* which describes the difficulties encountered in diagnosing the bearing dislocation of a mobile knee bearing[10]. A 54 year old woman experienced a sudden pain in her knee 1 year after surgery. Initial radiographic investigations did not identify that the knee bearing had dislocated and so she was returned home. When her symptoms remained, further radiographic investigations at a different hospital correctly diagnosed the dislocation of the bearing and the patient was finally operated on 17 days after the trauma. The dislocated bearing had migrated to the extra-articular popliteal area, making the surgery more challenging, the metallic components had become very scratched requiring a full revision to a total knee replacement, and the patient was in severe pain. Similar difficulties with diagnosis have been reported for mobile bearing knees in other case studies[11,12], and these issues would be mitigated by the use of a radiopaque bearing material.

Standard radiological follow-up protocol suggests that an initial postoperative assessment is performed immediately after surgery, and that this radiograph will then be used for reference at future follow-up visits[13]. A weight–bearing radiograph is ideally required for polyethylene joint replacement implants, however, a weight–bearing radiograph immediately after surgery causes discomfort for the patient. Enhancing the radiopacity of polyethylene eliminates the necessity of weight–bearing radiographs and potentially improves the quality of post-operative follow-up.

The above scenarios illustrate that there is a need for a polyethylene material with an improved X-ray visibility and performance. To create a radiopaque polymer normally additive would be mixed with the resin prior to consolidation[14]. However, oil-based fluids are partially miscible in polyethylene and can be diffused into the material to add additional functionalities to the polyethylene part. The diffusion approach to introducing an additive has many benefits; one of which is that for medical applications once the oil is contained within polyethylene because it is less soluble in aqueous body fluids it will be less likely to leach out. A common oil–incorporated polyethylene is vitamin E infused polyethylene. Orthopaedic manufacturers blend or diffuse α–tocopherols (vitamin E) into a polyethylene part to enhance the resistance of polyethylene to oxidation and improve the wear properties of the bearing[15] (e.g. Vivacit,

Table 1-1: The standard tests required by the regulatory bodies to confirm the safety of a novel polyethylene for medical use.

Properties	Test	Standard
Physical	Density	ASTM D1505, D732
	Differential scanning calorimetry (DSC)	ASTM F2625
	Oxidation induction time	ASTM D3895, D2009
Chemical	Fourier transform infrared spectroscopy (FTIR)	ASTM F2102, F2381
	Antioxidant concentration	ASTM F2695
	Dilute solution viscometry	ASTM D2857, F4020
	Swelling analysis	ASTM D2765, F2214
	Solgel	ASTM D2765
	Trace element	ASTM F648
Mechanical	Small punch	ASTM F2183
	Tensile	ASTM D2990, D638
	Compression	ASTM D695
	Fatigue	ASTM E647
	J-integral	ASTM D6068
	Creep	ASTM D2990
	Izod impact	ASTM D256
In vitro	Accelerated ageing	ASTM F2003
	Wear testing	ASTM F732

Zimmer-Biomet). Vitamin E infused polyethylene has more than 15 years of successful clinical history[15] and many clinical studies have confirmed its superior oxidative stability[16,17,18]. Lipiodol Ultra-Fluid is another oily fluid with a well-established clinical history and is an FDA-approved contrast agent[19]. Lipiodol contains 70% α–tocopherols[19] and due to the presence of iodine groups covalently attached to the hydrocarbon chains it can be detected using X-ray based imaging methods. Hence diffusion of Lipiodol into polyethylene has the potential to create a multifunctional oil-based polyethylene material which can provide both radiopacity and antioxidant properties.

Introducing a new material for long–term medical applications could cause new risks and complications, hence the regulatory bodies (MHRA, FDA) provide thorough guidance on the safety requirements and their approval is needed prior to clinical use of the material. Within the American and international testing standards (ASTM and ISO) there are many tests which need to be performed before introducing a new polyethylene onto the market. A summary of the key testing requirements is provided in Table 1-1. Regulatory bodies will refer to these standards when considering a new polyethylene for orthopaedics applications.

Considering the number of tests involved in the creation of new radiopaque polyethylene and the cost associated with the testing and development of a new material, it is crucial to ensure that the benefits in terms of clinical performance outweigh the risks associated with a new material. Therefore the effectiveness of any new polyethylene needs to be thoroughly

evaluated.

Last but not least, any new material needs to be commercially viable and there are manufacturing challenges that can occur in terms of scaling up of processes, costs in terms of both resource and time, as well as unexpected complications. For example, during the development of vitamin E infused polyethylene it was realised that the presence of the additive in the polymer resin reduced the efficiency of the cross-linking stage, which is performed at the end of the manufacturing process. It is therefore important that manufacturing factors are considered from the outset when investigating a potential new material for clinical application.

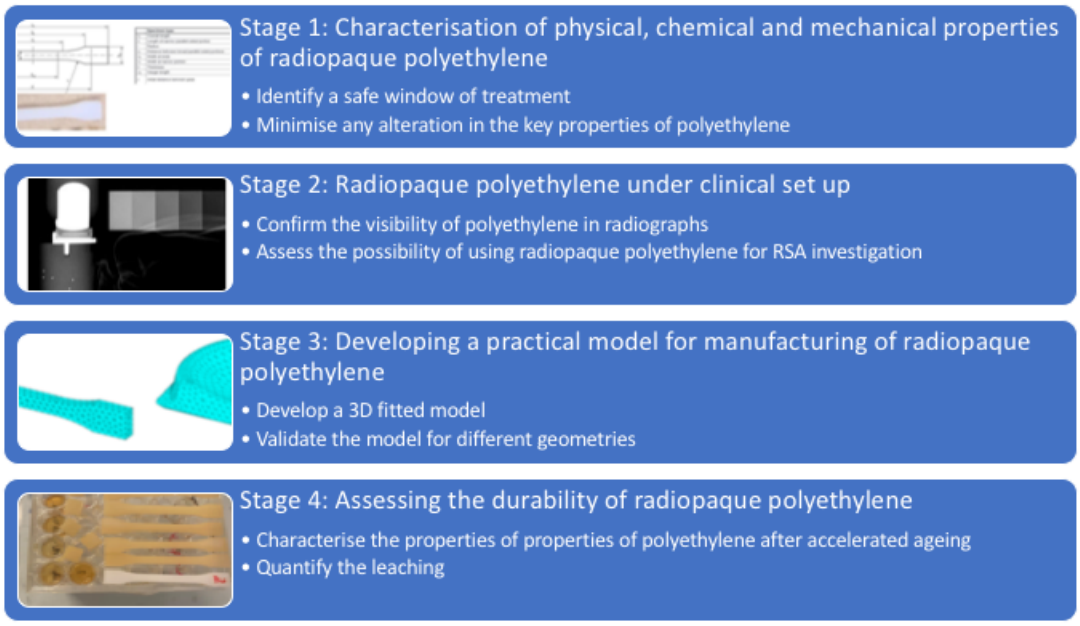

Figure 1-1: The four main stages of the research project

1.2 Thesis outline

This thesis aims to enhance the radiopacity of polyethylene for long-term medical applications by diffusing an FDA-approved contrast agent (Lipiodol Ultra Fluid) into polyethylene samples; this aim was achieved in 4 stages (Figure 1-1). Firstly, the mechanical, physical and chemical properties of this polyethylene were extensively investigated and safe window treatment was suggested. Secondly, to ensure the visibility of the radiopaque polyethylene under clinical imaging protocols, Lipiodol treated implants were radiographed under a clinical set-up at the Department of Radiology at Leiden University Medical Centre (LUMC) in collaboration with the LUMC Orthopaedics Department. Thirdly, the properties of the diffusion were investigated through the development of a finite-element (FE) model to assist with future manufacturing

planning. Fourthly, the long-term effects of Lipiodol treatment on the chemical, mechanical and radiological stability of the radiopaque polyethylene were identified.

1.3 Scope of the research

This thesis explores the question of whether a radiopaque UHMWPE produced using an oil-diffusion route could meet the clinical requirements for joint replacement and be commercially viable. The clinical requirements have been assessed in terms of the material properties, both before and after long-term use, but do not include wear or fatigue testing. The clinical imaging properties of the polyethylene have been examined, along with the mechanics of the diffusion. The biocompatibility and cellular responses to the material are important but beyond the scope of this research.

1.4 Note on the format

The thesis contents in terms of chapters and papers is shown in Table 1-2. Each paper is preceded by a 'Context' section and a 'Summary' section at the end of the chapter to contextualise how each paper is related to the overall research aim. Also included before each paper is a *Statement of Authorship* that outlines the candidate's contribution to to the published paper. The references for each paper are self-contained with a full bibliography at the end of the thesis.

Table 1-2: Overview of the thesis contents with reference to the research papers contained in each chapter.

Chapter	Paper in the chapter
Chapter 1: Overview of the thesis	
Chapter 2: Literature review	Medical-grade ultra-high molecular weight polyethylene: past, current and future. Published in Materials Science and Technology 34.16 (2018): 1940-1953. DOI: 10.1080/02670836.2018.1469455
Chapter 3: Mechanical properties	Characterisation of the physical, chemical and mechanical properties of a radiopaque polyethylene. Published in the Journal of Biomaterials Applications (2020). DOI:10.1177/0885328220922809
Chapter 4: Radiopacity under a clinical set up	Contrast enhancement makes Model-based Roentgen Stereophotogrammetric analysis possible for polyethylene implants. To be submitted to Acta Orthopaedica
Chapter 5: Model development	Practical model of the diffusion of oil-based fluids into polyethylene. Submitted to the Journal of Applied Polymer Science
Chapter 6: Longevity of polyethylene	Oxidative and Chemical Stability of Polyethylene is Enhanced by Oil Infusion. Submitted to the Journal of Biomaterials Applications (2020).
Chapter 7 : Discussion and further work	

Chapter 2

Medical-grade ultra-high molecular weight polyethylene: past, current, and future.

2.1 Context

The first paper presented in this thesis is a literature review that was written during the first year of the project. The review was submitted as part of the 2018 Materials Literature Review Prize of the Institute of Materials, Minerals and Mining run by the Editorial Board of Material Science and Technology Journal.

Appendix 6B: Statement of Authorship

This declaration concerns the article entitled:			
Medical-grade ultra-high molecular weight polyethylene: past, current and future			
Publication status (tick one) **Draft manuscript** [ ] **Submitted** [ ] **In review** [ ] **Accepted** [ ] **Published** [X]			
Publication details (reference)	Materials Science and Technology 34.16 (2018)- DOI: 10.1080/02670836.2018.1469455		
Copyright status (tick the appropriate statement) I hold the copyright for this material [ ] Copyright is retained by the publisher, but I have been given permission to replicate the material here [x]			
Candidate's contribution to the paper (provide details, and also indicate as a percentage)	The candidate considerably contributed to the The candidate significantly contributed to the all stages of this paper including, formulation of ideas and presentation of information in journal format. The review was drafted in 2017 and submitted to the journal as part of the 2018 literature review prize of institute of Materials, Mineral and mining society. Both supervisors (Dr Elise Pegg and Prof Richie Gill proof read the drafted paper and provided insightful feedback to improve the quality of the paper.		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	F.Zaribaf	**Date**	27/11/2020

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REVIEW

Medical-grade ultra-high molecular weight polyethylene: past, current and future

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ABSTRACT

Ultra-high molecular weight polyethylene is a semi-crystalline polymer (45–60%) with six decades of orthopaedic applications. This polymer has a high fracture toughness (30 kJ m^{-2}) which comes from the molecular weight and the chain entanglements. Adverse alteration of the properties may lead to the part's pre-mature failure. This paper reviews the current manufacturing methods, and their effect on the properties of the polymer. The review also focused on the attempts of enhancing the polymer properties. The main cause of failure is implant loosing owing to the polymeric wear particles. Many manufacturers have attempted to enhance the wear and oxidation properties of the polymer, and the outcome of the new technologies is critically reviewed. Finally, the review explores the potential for future developments.

ARTICLE HISTORY
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KEYWORDS
Ultra-high molecular weight polyethylene; vitamin E; radiopaque; packaging; sterilisation; crystallinity; cross-linking

This review was submitted as part of the 2018 Materials Literature Review Prize of the Institute of Materials, Minerals and Mining run by the Editorial Board of MST. Sponsorship of the prize by TWI Ltd is gratefully acknowledged.

Introduction

Ultra-high molecular weight polyethylene (UHMWPE) has a low friction, high resistance to wear, high toughness [1] and the polymer is bio-inert. Information with regard to the polymer wear and friction behaviour are summarised in Table 1. The linear wear rate of the acetabular cup is about 0.2 mm/year, and the friction coefficient of the polymer is lower than the other commonly used polymers such as polyamides, polytetrafluoroethylene and polyesters, and polyether ether ketone (ranged between 0.25 and 0.6, against steel, dry condition) [2]. On average, the friction coefficient of UHWMPE/metal is half of the PEAK/metal. Therefore, UHMWPE is an ideal material to use for long-term implants. However, many retrieval studies have shown evidence of severe oxidation and wear in UHMWPE implants. Oxidative stability and properties of UHMWPE are linked to the chemical structure, molecular weight, crystalline organisation and thermal history of the polymer [3]. It is crucial that any changes made to UHMWPE implants do not detrimentally affect their wear properties, oxidation resistance or fatigue strength.

From 2003 to 2016, about 796,636 total hip and 871,472 knee are implanted in England and Wales and the most common articulation used was polyethylene [8]. With the aging population, it is crucial to improve the longevity of the parts. Despite the successful clinical outcome of the most orthopaedic replacement, the longevity of the prosthesis is limited to approximately 15 years [9], and any modification can jeopardise the longevity of the part. Researchers are always trying to enhance the polymer properties and there have been significant new developments in this field. This review attempts to cover the new technologies. As the polymer changes, the body might react to the new polymer differently which needs to be understood to imply the alteration in the implant design. The current publications regarding the mechanical and material properties of the polymer, method of manufacturing, sterilisation and packaging of UHMWPE components, as well as examining common mechanisms of failures, new technologies as vitamin E UHMWPE and contemplating the future of the polymer.

Clinical uses of UHMWPE

This polymer was introduced clinically in November 1962 as an articulating surface for hip replacement implants, and in the late 1960s, it was first used for knee replacement [10,11]. In a total knee arthroplasty, UHMWPE provides articulating surfaces between the femur and tibia as well as between the femur and the patella [11]. Depending on the pathology of the disease, surgeons might prefer to use unicondylar knee arthroplasty [11]. There are 300 different designs of knee prostheses available around the world, and UHMWPE is used as the bearing materials in almost all of them [11].

The bearings are also used in other types of orthopaedic joints including shoulder, ankle and elbow

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Table 1. Physical and mechanical properties of UHMWPE (GUR 1050).

Properties	UHMWPE	References
Molecular weight (g mol^{-1})	36 million	Product data sheet
Density (g cm^{-3})	0.930	Product data sheet
Yield strength at 37°C (MPa)[a]	21	Product data sheet
Elastic modulus at 37°C (GPa)[a]	0.67	Product data sheet
Friction coefficient (Dry condition)[b]	0.12–0.15	[4]
Friction coefficient (Saline solution)[b]	0.05	[4]
Volumetric wear (Dry)[b]	5×10^{-5}	[4]
Fracture toughness (kJ m^{-2})	30.18	
Linear wear rate[c]	0.174 mm year^{-1}	[5]
Shore D hardness (21°C)	60–65	[5]
Surface roughness (mm, before wear testing)	0.01	[6]
Surface roughness (mm, after wear testing)	0.032	[6]

Note: MPa: Megapascal.
[a]Data gathered from the product data sheets and ISO 11542, ISO 527, ASTM790.
[b]Against CoCrMo.
[c]TiAl6V4 [7].

replacements [12–14]. Although these procedures are performed much less frequently than hip and knee replacements [12–14], the performance of these prostheses also relies on the polymer for motion and load bearing [15–18]. UHMWPE is also used in finger joint replacement [19]. The surgical considerations for small joint replacement are different to other joint arthroplasties [20]. In finger joint replacement, the implant acts as an internal splint allowing the soft tissues to rebalance [20]. In some designs of these prostheses, UHMWPE bearings have been used [20,21].

UHMWPE has also been used in spinal applications [22]. Chronic back pain can be treated by spinal fusion or disc arthroplasty. In both cases, UHMWPE may play an important role. UHMWPE fibre can be used for spinal fusion and UHMWPE bearings in disc replacement [23–25].

In the last few years, the polymer has been used for anterior cruciate ligament reconstruction [26,27]. In fibre form, it can be used for braided sutures [23]. The modulus of polyethylene fibre is as high as 222 GPa and the strength of the fibre is 8 GPa [28]. Porous polyethylene (pore diameter between 100 and 250 mm) can be used for facial reconstruction [29] and bone defect replacement [30–32]. Porous PE (Medpor) (Medpor Biomaterial; Porex Surgical, Newman, GA) has an application in craniofacial reconstruction [30,33,34], because it can closely mimic porous cancellous bone tissue [31]. This type of polyethylene has the same hardness as cancellous bone tissue and it can be trimmed and modified during the surgery. The polymer makes up 54% volume of the implant and rest of the implant are filled with air. The pores structure allows the bone to ingrowth through the implant with collagen deposition. Therefore, the implant is resistance to infection. Porous polyethylene is able to deform by surrounding tissue [34]. The tensile strength of porous polyethylene is as high as 4.1 GPa, hence polymer is able to resist stress and fatigue [30].

Resin manufacturing

The formation of resin is the first step towards the manufacturing of an UHMWPE component. The resin can be polymerised by the Ziegler–Natta process using ethylene and hydrogen gases and titanium tetrachloride (a catalyst) [35]. A solvent is required for heat and mass transfer [35]. The polymerisation of the resin requires a specialised production plant capable of handling dangerous chemicals. Hence, there are only two companies capable of making resins. Medical-grade UHMWPE is free of calcium stearate and has a higher purity requirement as set by ISO 5834-1 [7]. Type 1 and 2 resins (GUR 1050, GUR 1020) are produced by a German company called Celanese, and Basell used to produce type 3 resin (1900). Although the manufacturing method is identical, a slight variation in the molecular weight of the different resins was reported [36]. This variation can be associated with the catalyst package and the polymerisation condition. Table 2 summarises the differences between the resins. Furthermore, a slight variation between the resin morphology was reported. Type 1 and 2 resins appeared to be more lamellar while type 3 resin has a spherulitic morphology. Type 3 resin is no longer in the market.

The molecular weight of the resins affects their mechanical properties and their wear abrasion resistance. Clinical data showed that 1900 has a superior resistance to wear and oxidation but the lowest mechanical properties among the three resins. While, as Table 2 the experimental data showed no statistically significant difference between the oxidation resistance of the resins [37]. The wear resistance of 1050 is slightly better than GUR 1020, while GUR 1020 has a better impact strength and toughness.

Manufacture of UHMWPE components

The second stage towards making a component is the consolidation of the resin under elevated temperature and pressure. Due to its high molecular weight, the polymer has a high melt viscosity and it is not able to flow like lower molecule weight polyethylene [36]; UHMWPE has a zero melt flow index. Hence, ram extrusion and compression moulding are two typically used methods to produce semi-finished or finished

Table 2. Physical properties of medical-grade UHMWPE resins.

Properties	Type 1	Type 2	Type 3
Average molecular weight ($\times 10^6$, g mol^{-1})	3.5	5–6	> 4
Particle size (mm)	140	140	300
Tensile modulus (MPa)	720	680	750
Impact strength (KJ m^2)	> 210	> 130	> 65
Yield stress (MPa)	> 17	> 17	19

Note: MPa: Megapascal.

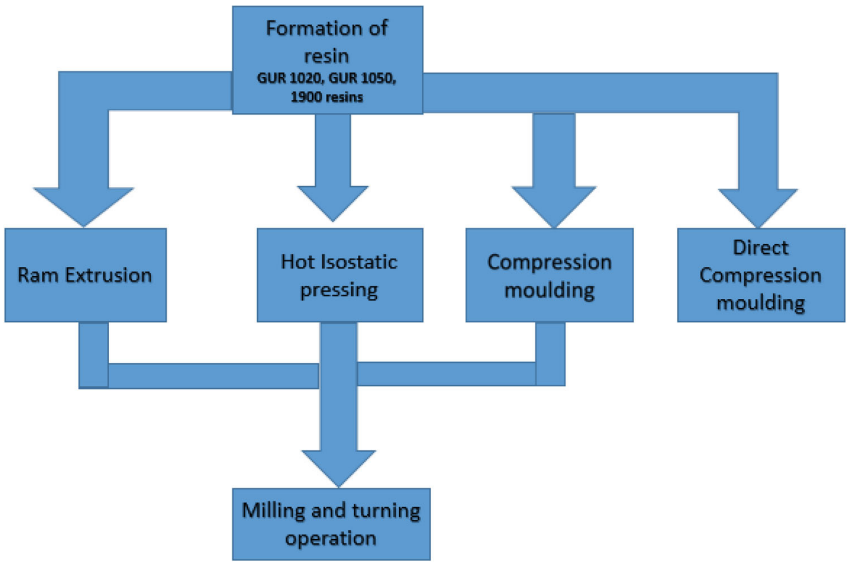

Figure 1. The processing steps involved in making an UHMWPE part.

components [3,36]. The machining temperature needs to be closely monitored as the UHMWPE can be easily damaged by excessive heat [38]. Figure 1 shows the manufacturing steps. Machining is able to change the surface and subsurface properties of the polymer. A higher machining speed leads to a greater mechanical degradation and a lower wear resistance. However, no significant correlations have been found between the machining parameters and the wear coefficient [39,40].

The difference between parts made from extrusion and compression is insignificant, and in both cases, the mechanical properties exceed the ASTM F648 requirement [41]. The main difference between the ram extruded and compression moulded parts is in the morphology of the segments [3]. TEM images showed that ram-extruded polymer lamellae are aligned along the extrusion direction while compression moulded samples showed the random orientation of the crystalline lamellae. Lack of preferred orientation in lamellae enhances the fatigue resistance and crack propagation of the polymer which are summarised in Table 3.

Some manufacturers prefer to consolidate the resin into semi-finished parts using an individual mould, avoiding intermediate machining steps. Direct compression moulding leads to a smooth surface finish with no machining marks [3]. Tensile properties of direct compression moulding parts are suggested to be higher than other methods [43–45]. This is because compression moulding can be performed under a very high pressure (300 MPa), hence there are few/no fusion defects which leads to up to a 40% increase in the yield strength without decreasing the impact strength or toughness of the polymer [3,38]. Another possible reason for the better tensile properties is the greater percentage of crystallinity of directly moulded parts which is nearly 72%. This can be associated with lower risk of oxidation in the component and a better resistance to post-irradiation aging. Microscopic images from the surface of the component also support that direct compression moulded parts have an ability to resist oxidation. The ultimate tensile strength of the samples can drop by 60% over a range of oxidation [42]. This can be because spatial variations in the degree of consolidation of ram extruded the bars along the radius which can be indicated by the presence of inter-particle regions and fusion defects [42,44].

Table 3. Fatigue and crack propagation of ram-extruded and compression-moulded polymer.

Properties	Ram extrusion	Compression moulding
ΔK_{th}(MPa $\sqrt{m}$)[a]	1.3–1.7	1.2–1.8
$\Delta\delta_t$ (mm)[b]	62.8	70.4

Source: Adapted from [42].
Note: GUR 415 resin which no longer has a medical application.
[a]Crack opening displacement.
[b]The fatigue threshold.

A study by Bankston et al. investigated the wear properties of samples manufactured using direct compression or another form of machining (either ram extrusion or compression moulded part). Clinical studies on two groups of patients, assigning 54 patients to each group with no significant difference between in the average age, weight (average weight = 161 pounds and age = 66 years old) for an average follow-up of 6.7 years showed the average linear wear rate per year was 0.05 mm for direct compression moulding and 0.11 mm for machined polyethylene [46]. Retrieved implants show that direct compression moulded samples have a higher chemical stability and little to no oxidative damage and no evidence of delamination or discoloration, in retrievals after four years [46–48]. However, the

number un-fatigued parts dropped sharply as the implantation time increased (32% for moulded components and 36% of the machined component). Direct compression moulded is also capable of producing unique designs, but it is a time-consuming and expensive method [48].

Cross-linking

The most common failure mechanisms are aseptic loosening and dislocation (82% of cases) which are associated with wear resistance of polyethylene. To improve the wear resistance of UHMWPE, manufacturers have attempted to increase the cross-linking density of the polymer [49]. The conventional form is not cross-linked [50]. Cross-linking significantly increases the wear abrasion resistance, and reduces the mobility of the free radicals [51]. As Table 4 shows the wear rate of conventional polyethylene is six times more than the highly cross-linked polymer. Experimental data showed that cross-linking improves the wear properties of the polymer up to 90% [54] (Table 4). Furthermore, a higher abrasion resistance in cross-linked polyethylene enables surgeons to use thinner components, which can have clinical advantages. For instance, in hip replacement, this allows for the use of a larger femoral head, which reduces the risk of dislocation [51]. There are three ways of cross-linking polyethylene: radiation, organic peroxide chemistry or using saline chemistry [51]. However, only the two first methods are clinically approved as saline chemistry involves the use of harsh chemical.

In the first two methods, cross-linking is achieved by the formation of active sites at the end of the chains. The active sites (free radicals) can recombine to form trans-vinylene bonds [55]. Gamma irradiation is the most common way to cross-link UHMWPE; however, it is also possible to use electron beam irradiation [51]. Gamma irradiation can also be used to sterilise components [56] as discussed in Section 2.8; the peroxide method involves its decomposes by a free radical reaction that leads to the formation of cross-links between chains at the elevated temperatures associated with the manufacturing process [3].

There are some concerns with both the methods. UHMWPE is semi-crystalline and free radicals trapped in crystalline regions are not mobile enough to react with each other [55]. However, over time, the free radicals diffuse slowly to the amorphous regions and can lead to degenerative oxidation [55]. Similarly, there are concerns about the oxidative instability of the peroxide cross-linked version [55].

Even though increasing cross-linking density increases the abrasion resistance of the polymer, however, the cross-linked polymer is less tolerant to severe clinical conditions and less resistance to crack propagation [54,57]. Table 4 shows that the mechanical properties of the conventional and cross-linked polymer, elastic modulus, ultimate tensile strength, yield strength and ductility of the polymer will be reduced as cross-linking density increases. The cross-linking density increases with radiation and 100 kGy is the saturation point.

Any alteration in the microstructure of the polymer changes the mechanical properties. Cross-linking reduces the plasticity of the polymer which leads to a 32% reduction in fracture toughness (K_c). Fracture toughness determined the fatigue crack propagation of the polymer. Retrieval analysis on four highly cross-linked acetabular cups showed that there is no significant sign of oxidation; however, brittle fracture failure was the main cause of failure in all the samples [57].

Histological studies have shown cross-linking reduce the biological response to the wear particles and a lower amount of multinucleated has been found [55,58]. Fisher has shown that cross-linking generates a larger amount of small particles [59]. Larger particles cannot be ingested by the macrophages, so they will be surrounded by multinucleated foreign body giant cells, which are the hallmark of a chronic inflammatory process. However, the finer particles induce more macrophage and inflammatory mediators, resulting in more osteolysis (bone resorption means more bone resorption) [59].

Overall, there is a lower ductility and fatigue resistance associated with extensive cross-linking [60]. Furthermore, highly cross-linked UHMWPE has a lower toughness and mechanical strength. Therefore, it is desirable to limit the degree of cross-linking and keep it local to the surface of the polymer to retain the

Table 4. Physical properties of conventional and highly cross-linked UHMWPE [52,53].

Properties	Conventional	Cross-linked at 30 kGy	Cross-linked at 50 kGy	Cross-linked at 75 kGy	Cross-linked at 100 kGy
Cross-link density ($\times 10^{-4}$ mol dl^{-1})		105.1	158.7	180.8	197.6
Molecular weight between cross-links (g mol^{-1})		9500	6300	5800	5060
Crystallinity	53.3 ± 0.9	47.5 ± 1.2	48.5 ± 0.7	47.7 ± 0.5	47.9 ± 7
Oxidation index[a]	0	0.013	0.015	0.017	0.030
Oxidation index[a] (after 10 weeks aging)	1.2	1.25	0.1.4	2.40	2.9
Fracture toughness (K_c, (MPa $\sqrt{m}$))	4.0 ± 0.5	4.5 ± 0.02	3.0 ± 0.6		
Elastic modulus (MPa)	648	737	570		
Yield strength (MPa)	22 ± 0.4	19.6 ± 0.5	19.6 ± 0.5	19.9 ± 0.1	20.2 ± 0.1
Ultimate tensile strength	50 ± 1.6	47.1 ± 4.2	37.1 ± 3.2		
Wear rate (mg million cycles^{-1})	9.8 ± 0.7	9.1 ± 0.3	4.8 ± 0.7	2.5 ± 0.4	1.6 ± 0.3

[a] Keton oxidation.

bulk mechanical properties [61]. Oxidation is the main concern with cross-linking. Failure analysis of retrieved UHMWPE implants regularly shows signs of surface cracking, abrasion, scratching and pitting marks, which can be owing to oxidative degradation [54,62]. Hence, different methods have been developed to increase the oxidative stability of cross-linked UHMWPE, which is covered in the next section.

Thermal treatment

As mentioned, free radicals will be formed during cross-linking or sterilisation of UHMWPE, reducing the oxidative stability of the polymer [63,64]. One method used to reduce the amount of free radicals is post-irradiation thermal treatment which at the same time releases residual stress due the thermal history induced by ram extrusion or compression moulding [63]. Two common thermal treatments are remelting and annealing. Remelting is when the temperature is elevated above the melting point (approximately 150°C) leads to complete melting of the polymer crystallites, allowing the free radicals trapped in the crystalline phase to diffuse out [3]. Usually, remelting reduces the amount of residual radicals to undetectable levels. Annealing is when the temperature rise does not exceed the melting point, hence, it leaves a measurable amount of free radicals in the polymer [65]. Free radicals can be detected from using a type of spectroscopy (electron spin resonance (ESR)) which is able to detect the unpaired electron. There are three types of free radicals: alkyl, allyl and polyenyl [66].

The main concern with any thermal treatment is the possibility of reducing crystallinity during the cooling process as there is no pressure applied [67]. With current processing technologies, applying pressure is not feasible [55,68]. The crystallinity of UHMWPE is associated with the fatigue crack propagation resistance [69]. Crystallinity can enhance the oxidative resistance of the polymer. This is because the oxygen is only able to diffuse into the amorphous region. The oxidised polymer is more brittle and less resistance to fatigue crack propagation [70]. Remelting has been shown to significantly reduce the degree of crystallinity [71–74], and the crystallinity reduction can be as high as 10% [74]. While remelting determinately affects mechanical properties of the polymer, annealing showed no statistically significant decrease in the crystallinity ($p > 0.005$) and many of the mechanical properties of the polymer including yield, ultimate strength and fatigue properties remain unchanged [3,68].

However, results obtained from aging studies are controversial. Muratoglu and co-workers investigated the wear and oxidation properties of remelted and annealed cross-linked UHMWPE [66]. As was expected, initially the thermally treated UHMWPE had better wear properties than the untreated samples. However, after artificial aging, residual free radicals in annealed samples were detected by ESR but not in the remelted samples [66]. Free radicals cause oxidation and reduce the ductility and wear resistance of the polymer. A study of real-time aged samples also showed a reduction in oxidative stability of annealed UHMWPE after aging [75]. In both studies, a significant oxidation was observed on the surface of the UHMWPE test samples.

Many different studies have calculated the linear wear rate of the polymer after thermal treatment using hip simulators. There is a broad distribution in wear rates of different studies [76–78], which is likely to be owing to variations in design, metallic materials and the size of the femoral head. Nevertheless, all studies demonstrated a high reduction in wear rate for the highly cross-linked and annealed UHMWPE compared to untreated UHMWPE.

The clinical data have detected a measurable amount of oxidation of remelted retrieved parts which was significantly higher than *in vitro* studies. A possible explanation could be the test lubricant and the loading conditions of *in vitro* studies [79–82]. It has been proved that UHMWPE is able to absorb the lipid with synovial fluid which alters its mechanical properties [79,83,84].

To summarise, free radicals were generated during cross-linking and so thermal treatment was applied with the intention of reducing the amount of free radicals and increasing the oxidative stability of the polymer. The first highly cross-linked UHMWPE was irradiated with a high dose followed by melting or annealing. However, the material properties of the polymer underwent a significant change after remelting [63], and annealing did not eliminate all the free radicals [85]. In the second generation, high cross-linking levels were achieved by repeating the irradiation and annealing steps to allow the free radicals to recombine completely [86]. This method reduced the amount of free radical to an undetectable level, and aging studies also showed a very low amount of free radicals. However, clinical studies on knee retrievals showed pitting and subsurface white banding and cracking [87,88]. Studies hypothesised this as a result of low crystallinity and fatigue strength. This unsatisfactory result led to a search for an alternative to reduce the influence of free radicals. The next section reviews the use of anti-oxidants to prevent oxidative degradation.

Anti-oxidants

Vitamin E is a natural anti-oxidant, which is able to suppress the free radicals which cause oxidation by reducing both alkyl and peroxy radicals, and consequently improve the wear resistance of the polymer [89,90]. The addition of vitamin E does not require any post-irradiation thermal treatment [91].

There are two methods of incorporating vitamin E within UHMWPE (Figure 2). In the first method,

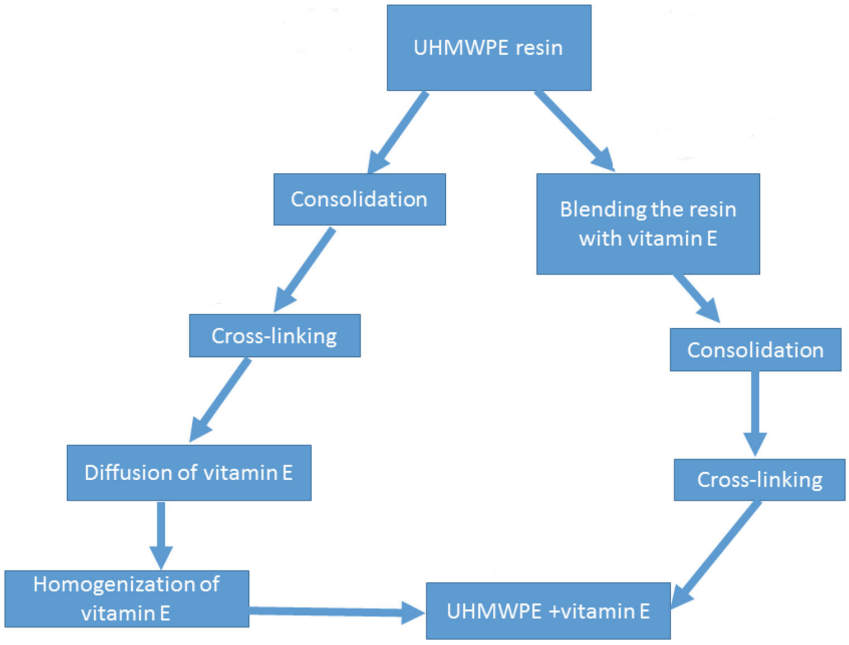

Figure 2. Schematic illustration of the two different methods used to incorporate vitamin E. The first method involves the diffusion of vitamin E into consolidated and cross-linked UHMWPE parts, and the second is blending of the vitamin E with the UHMWPE resin before consolidation.

vitamin E is blended with UHMWPE before consolidation, a process that does not affect consolidation, [92], as a free radical scavenger and it can inhibit the formation of cross-links. Hence, the vitamin E concentration in the blend should be limited to less than 0.3 wt-% [93]. The alternative method is diffusion of the vitamin into UHMWPE after cross-linking [91], and so cross-linking efficiency is not affected. On the other hand, UHMWPE goes through irradiation without any anti-oxidant protection and an extra homogenisation step is required to obtain an adequate concentration of vitamin E throughout the part. Diffusion and homogenisation require an elevated temperature to facilitate the diffusion of vitamin E, though the temperature is kept below the melting point, so it does not affect the crystallinity of the polymer [92].

Overall, *in vitro* studies have confirmed that vitamin E increases the oxidative stability of irradiated UHMWPE, so components are now used clinically [69,91,94–97].

Knee simulator studies have suggested that vitamin E containing UHMWPE (GUR 1050) parts have a lower wear volume compared to the conventional polymer parts, suggesting that anti-oxidants improve the wear resistance. The volumetric wear of conventional polymer is 41.3 mm^3 and 27 mm^3 for vitamin E added polymer (max load 2600 N, 5 million cycles) [98].

Vitamin E may have an effect on the realignment and recrystallisation of the polymer chains. The individual polymeric chain stems are able to rotate with respect to each other, leading to a change in the lamellar structure and also crystals can grow to a larger extent [99]. Okubo et al. have shown that stress-induced crystallisation of UHMWPE is hindered by the addition of vitamin E. X-ray diffraction results suggested the realignment of the molecular chains within the amorphous phase was the cause of these changes [100].

The tensile properties of the vitamin E infused polyethylene changed, 10% increase in yield strength and 12% drop in ultimate tensile strength of the polymer [101]. There was a 25% increase in fatigue crack propagation of the polymer [101]. A possible explanation is that vitamin E can be a plasticising agent and lead to an increase in the chain mobility which can be the reason for the improved fatigue strength [99].

The mechanical and fatigue strength of vitamin E infused polyethylene is greater than the highly cross-linked UHMWPE [96], and there was no significant difference between the mechanical properties of vitamin E treated and untreated samples. Vitamin E diffused UHMWPE led to no significant alteration in the stress intensity factor of the polymer after artificial aging, equivalent to five years of natural aging [69,94]. Stress intensity factor indicates the fatigue crack propagation of the polymer. This can be because one method that materials decrease the localised stress at the crack tip is by plastic deformation. Vitamin E can act as a plasticising agent and increase the ductility and chain mobility of the polymer. Furthermore, as there is no thermal

treatment (remelting or annealing) after adding vitamin E; hence, the crystallinity of the polymer is going to be intact preserving the mechanical properties of the polymer.

Animal and cell studies did not detect any adverse biological response to vitamin E infused part, and clinical data to date support the *in vitro* results. Hence, it can be concluded that vitamin E stabilisation is a promising alternative to thermal treatments [102].

Vitamin UHMWPE was clinically introduced in 2007, and short-term clinical data (up to three years) show that there is no specific complication with this type of polymer and there is no significant difference in the wear rate of UHMWPE and highly cross-linked polymer [103]. Clinical data to date support there are no negative short-term complications with this material and low concentration of free radicals can be an indication of long-term oxidative stability. However, there is no information available regarding the performance of the parts beyond 10 years.

Packaging and sterilisation

Finished UHMWPE components need to undergo packaging and sterilisation before clinical use. Figure 3 shows the current packing methods used.

The most common way to sterilise UHMWPE is high energy radiation [104]. Typically, a nominal dose of 25–40 kGy gamma sterilisation is used [105]. As mentioned previously, cross-linking can be formed using irradiation and the main concern was that a high dose of radiation in air promotes oxidative degradation and loss of desirable properties [106]. To avoid any oxidation, manufacturers perform the irradiation in a vacuum or under an inert gas such as nitrogen or argon [107,108]. Since there is no oxygen available, the free radicals will recombine and form UHMWPE cross-links rather than oxidise the UHMWPE.

Another method of sterilisation is ethylene oxide sterilisation (EtO). EtO has a high toxicity and is able to neutralise bacteria, spores and viruses. EtO can be used for UHMWPE parts as there are no constituents which are able to react or bind to the toxic gas. Therefore, EtO has no substantial influence on the mechanical, physical and mechanical properties of the polymer [109,110]. Sterilisation of UHMWPE is achieved by diffusion of EtO into near surface regions (up to 2 mm depth), then allowing it to diffuse out [80]. It is important that all ethylene diffuses out of the polymer as it can be toxic for biological tissues. Studies on retrieved implants have shown that EtO-sterilised UHMWPE ex-plants have a less surface damage and delamination compared to those which underwent gamma sterilisation [111].

The third possible method of sterilisation is gas plasma (GP), a surface sterilisation method that relies upon ionised gas for deactivation of biological organisms [104]. Either low-temperature peracetic acid GP or low-temperature hydrogen peroxide GP can be used. Many different studies show that GP has no effect on the mechanical, chemical and physical properties of the polymer [112–115]; however, it has been shown that the mechanical properties of porous UHMWPE and UHMWPE fibre can change as it goes through GP. Studies have hypothesised this is because GP reacts with the surface of the polymer, and porous or fibrous UHMWPE has a higher surface area [110]. The main advantage of GP is that it does not leave any toxic residue in the polymer and does not create free radicals.

Different manufacturing procedures tend to use different methods of sterilisation and none of these options can be considered as the preferred method. All these methods have some disadvantages; radiations create free radicals, while there is a possibility that EtO leaves toxic residues within the UHMWPE; however, to the date of this study, there is no case of toxicity. Finally, GP might modify the surface chemistry of the polymer [110].

Packaging is important, as the UHMWPE components are usually stored before implantation. There are three clinically approved classes of packaging, including gas permeable packaging (class I), multi-layer film barrier packaging (class II) and barrier packaging (class III). All the manufacturers are entitled to show an expiration date on the packaging. The main difference between the type of packing is the polymers used in the packages. The polymeric materials of each type of packaging have been explained in Figure 3.

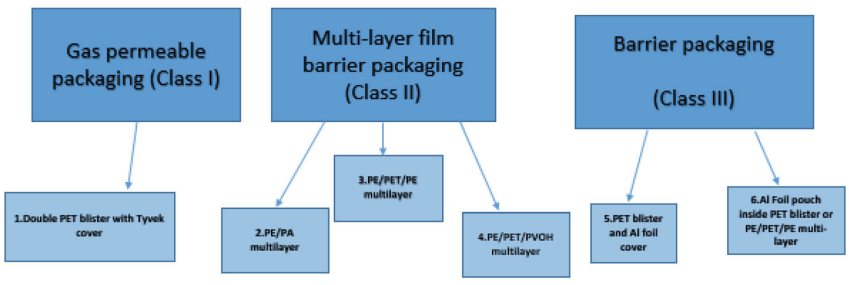

Figure 3. There are three different types of packaging for an UHMWPE part including gas permeable, multi-layer film barrier packaging and barrier packaging.

A study by Costa et al. examined the oxidation level of the parts packed using one of the three classes [116]. The oxidation index was calculated based on American Society for Testing and Materials (ASTM). According to the standard, the oxidation index of the parts should be less than 1 to be suitable for clinical application. Before the expiry date, the oxidation index of the parts in all three different types of packaging was less than 0.5 and there was no statistically significant difference between the value of the oxidation index of different groups ($p < 0.05$ for Mann–Whitney tests). On the other hand, significant oxidation was associated with class I and II expired packaging but not class III [116].

Overall, all three types of packaging meet ASTM requirements and none of them causes a significant alteration in the chemistry of the polymer unless the packaging is expired.

Radiopaque UHMWPE

At the time of this study, there was no commercially available bulk radiopaque UHMWPE. However, Bogie et al. used bismuth trioxide to develop a novel radiopaque UHMWPE fibre [24] for an application in a growth-guidance system for early-onset scoliosis. In this study, 20 wt-% Bi_2O_3 particles were blended into each UHMWPE fibre [24]. This polymer is available on the market under the commercial name of Dyneema.

However, this product is relatively new and there are not many publications examining the effect of Bi_2O_3 on the mechanical properties of the UHMWPE. Bogie et al. referred to unpublished data which confirmed all the samples containing Bi_2O_3 survived the fatigue test ($N = 5$ million cycles, $F = 1350N$) [24].

Recently, Roth et al. studied the effect of the addition of Bi_2O_3 on the fatigue and tensile properties of UHMWPE woven cables [117]. Their study suggested that the tensile and fatigue strength of the UHMWPE were not deleteriously affected by the addition of Bi_2O_3 particles. Contrary to expectations, a leaching study did not find a detectable release of Bi_2O_3 in the *in vitro* environment [117]; however, the animal testing detected particles of Bi_2O_3 in different tissues [24]. One possible explanation for this difference is that in this study, the samples were not loaded, and furthermore, the saline solution used does not accurately represent the *in vivo* environment [118].

There are no clinical studies available with regard to the radiopaque UHMWPE fibre. Histological studies on the surrounding tissues of the animals showed no chronic inflammation to the radio-opacifying agent [24],

In a different study, Kozakiewicz et al. attempted to make a radiopaque UHMWPE using TiO_2 [119]. Their experimental data suggested that some of the mechanical properties of the polymer including hardness, tensile modulus and strength of modulus of the polymer decreased. Also, even though a slight radiological detection was possible, the radiopacity of this polymer was not comparable with metals.

A few patents have disclosed methods to create radiopaque UHMWPE [120,121]. One of them suggested combining UHMWPE with oil-based fluids containing heavy elements such as iodine [120]. Another patent by U.S. researchers used an ion plasma deposition coating to make UHMWPE visible in X-ray images [122]. One of the limitations with the use of a coating is its adhesion strength to the main component, though this is an interesting approach which could have potential for further research.

Critique and research gaps

UHMWPE is the bearing material for most of the orthopaedic replacements. The polymer has a limited radiopacity wear resistance and antimicrobial properties which, if improved, could enhance the longevity of the implant.

One of the limitations of UHMWPE components is lack of radiopacity. Therefore, early diagnosis of failure can be hard and it is not possible to monitor the implant positioning during the surgery. Currently, there is no clinically approved radiopaque UHMWPE which can be used for bulk surgical implants. The only radiopaque UHMWPE is a fibre and the technology cannot be used to manufacture UHMWPE components. Therefore, enhancing the radiopacity of the polymer could have significant clinical benefits. One way to enhance the radiopacity of the polymer is by introducing a group like iodine which has a high radiopacity. As this review covered, vitamin E is an oil-based fluid which has been used to increase the oxidative stability of the polymer. Vitamin E had no detrimental effect on the mechanical properties of the polymer. It can be hypothesised that other oil-based fluids are also able to diffuse into the polymer. Lipiodol is another oil-based fluid with similar properties to vitamin E and the fluid contains iodine, so it is radiopaque. Lipiodol can be diffused into the polymer and enhance the X-ray attenuation of the part [120].

Wear of the UHMWPE bearing is the major cause of failure and a key limitation. Hence, many researchers have attempted to enhance the wear resistance of the polymer to reduce the production of wear particles and enable implants to have greater longevities. Introducing cross-linking and vitamin E to the polymer using thermal treatment are ways of enhancing the wear resistance; however, wear is still a common cause of failure. A few patents have been disclosed which aim to enhance the wear resistance of UHMWPE parts. One of them suggested the polymer resin can be irradiated before consolidation to have a better control on the

radiation and achieving a higher degree of cross-linking [123]. A possible complication is that a high degree of cross-linking reduces the ductility of the part, hence it is preferable to limit the cross-linking to the surface of the polymer, not the bulk. Another possible challenge in this method is that radiation may enhance the rate of oxidation due to the formation of free radicals. Although most of the time the part will be stored in a non-oxidative environment, oxidation can occur *in vivo* and is increased by certain macromolecules in the synovial fluid such as Squalene [124]. The feasibility of running the consolidation and manufacturing process in an inert environment is low.

Another patent suggested that the use of sequential irradiation followed by sequential annealing is able to reduce the oxidation and enhance the wear resistance [125]. This is because each radiation can be low while the total dose of irradiation is sufficient enough to achieve a high degree of cross-linking. A possible limitation of this method is controlling the location of the cross-linking. To retain the mechanical properties of the polymer, cross-linking should be limited to the surface of the polymer. Micro-injection moulding attempted to be used to control physical and chemical properties of the polymer and enhance the wear resistance [126]. Due to the high molecular weight of the polymer, this method can be very expensive.

Most of the methods that enhance the wear resistance of the polymer may lead to the reduction of some other mechanical properties of the polymer. The fatigue crack propagation resistance of cross-linked UHMWPE is approximately 40% lower than the none cross-linked polymer [60,94]. This is a source of concern, especially where the implant is subjected to a high stress. Hence there should be a way to enhance the fatigue resistance of the polymer without jeopardising the wear resistance. Currently, manufacturers try to limit cross-linking to the articulating surface, so the mechanical properties of the bulk stay intact. This method is not feasible for curved surfaces. A study by Oral et al. attempted to manipulate the degree of cross-linking by using a spatially variant concentration profile of vitamin E during irradiation [127]. The surface of the polymer has a lower concentration of vitamin E than the bulk and their experimental data were promising. Using materials with a higher fatigue resistance can be very beneficial as it means a thinner part can be used. Using thin parts means surgeons would be able to preserve a higher amount of the bone stock and reduce the chance of dislocation [127].

Bacterial infection is a post-operative complication and one of the main cause of early failure [128,129]. Around 4000–8000 infected knee implants require surgical revision annually [130]. Due to lack of blood supply around the implant, it can be hard to deliver a drug to the site of surgery. Localised drugs and antibiotics are normally used after the surgery. This means patients will be exposed to a high dose of drugs which can be dangerous [131]. Furthermore, this is not a long-term solution. Hence, making an implant with sustained antimicrobial ability can be very beneficial. So a few studies have attempted to use UHMWPE as a drug delivery device [132,133]. A study by Kumar et al. attempt to coat the inner surface with some drug-loaded biodegradable polymer [132], so as the polymer wear off drugs will be realised at the site of surgery. In this case, retaining the tribological and mechanical properties of the polymer can be very challenging. Muratoglu et al. tried to mould UHMWPE with vancomycin which is an antibiotic; their results showed that the presence of the drug reduced the ultimate strength and the impact toughness of the polymer. Antimicrobial properties of UHMWPE can also be enhanced using ion implantation. The experimental results showed that the bacterial adhesion reduces up to 90% depending on type of the ion [134]. There is no published information available with regard to alteration in the mechanical properties of this type of resin polymer.

This section attempted to cover the gaps of research and how UHMWPE can be modified to enhance the mobility and quality of life of the patients. Radiological limitation of UHMWPE led to difficulty in implant positioning and post-operative follow-up. Wear resistance and fatigue propagation of the polymer should be improved and antimicrobial UHMWPE can reduce the risk of revision surgery.

Conclusion

Figure 4 shows the number of orthopaedic procedure increases every year. Therefore, this paper has reviewed and explained the clinical applications of UHMWPE, how polyethylene implants are manufactured and the concerns associated with them in orthopaedic replacement. Ultra-high molecular polyethylene is the material of choice for the orthopaedics-bearing materials. The experimental data showed that the polymer has a friction of approximately 0.5 ; however, polymer wear properties are limited and the resistance to wear decreases with time. A possible explanation is oxidation caused by free radicals. Oxygen is able to diffuse through the polymer even very slowly. Oxidation causes breakage of the polymer chains, making the polymer less ductile. Plastic deformation of the polymer is a way that polymer resists the fracture crack propagation. Therefore, as the ductility decreases, the polymer resistance to crack decreases.

Another common cause of failure is wear and researchers have attempted to enhance the wear properties of the polymer, which can be achieved by introducing the cross-linking. Depending on the amount of cross-linking, the wear resistance of the polymer can be

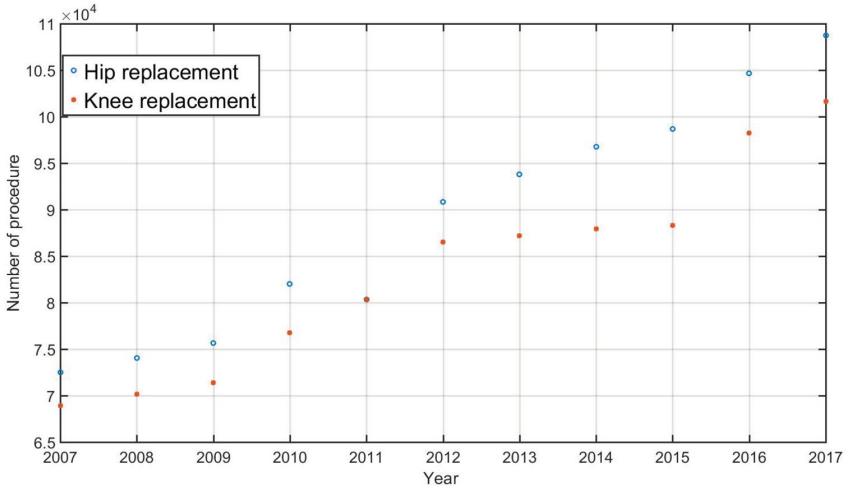

Figure 4. The number of hip and knee replacements in England and Wales.

enhanced by 90%; however, cross-linking will reduce the resistance of the polymer to crack propagation and fatigue. The radiation dose of 50–100 kGy is required for cross-linking. Also, free radicals are required to form cross-links. If there is a free radical trapped inside the crystalline areas of polymer, over time it can react with oxygen and cause oxidation.

Thermal treatment was introduced to reduce the amount of the free radicals inside the polymer. Post-irradiation melting leads to the reduction in the crystallinity which reduces the other properties of the polymer.

Alternative approaches have been developed to enhance the polymer oxidation and wear resistance and one of them is incorporating vitamin E. Experimental and clinical data so far suggested that there is no short-term complication. Vitamin E was clinically introduced on 2007 and there is no long-term information available.

Even though wear and oxidation reduced significantly since the first generation of bearing, they are still cause a major concern. Radiopacity of the polymer can be enhanced to improve the wear analysis of the implants as well as diagnose early failure.

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Disclosure statement

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2.2 Summary

Since the paper was published many research group across the world attempted to add additional functionalities to polyethylene. For example, cross-linked powder reinforcement used to enhance oxidative stability and wear of polyethylene[224]. Many studies reinforced UHMWPE with carbon nano-onions, carbon nanofibres, graphite, hydroxyapatite and collagen to increase the mechanical and thermal properties of polyethene and the initial outcome is very promising[34,40,200,143,150]. Another novel UHMWPE composite is when titanium alloys were added to polyethene resin which made the material more suitable for additive manufacturing[151]. Additional functionalities like antimicrobial properties was also introduced to polyethylene materials using bupivacaine or polyphenol blends[49,58,50] which can be very beneficial to prevent any post operation infection. Further studies and evaluation conducted on vitamin E incorporated polyethylene and now there is more information available on the application-specific performance of vitamin E polyethyelne (shoulder arthroplasty and many different designs of hip implants)[4,39], and the reasons behind the revision of the parts[41].

The literature review identified several areas in which further research could improve the properties polyethylene for long term medical application, but also highlighted some important lessons from the past in terms of the safety and clinical function. The review confirmed the novelty of radiopaque polyethylene parts and their potential for orthopaedic application. Following on from the literature review, the objectives for the research project were defined as:

1. Understand the influence that treatment with iodised oil has on the mechanical, physical and chemical properties of the polyethylene:

    - To be achieved by examining a variety of treatment parameters and characterising the properties of the polyethylene. So that the clinical applicability of the results can be interpreted, results will be compared with untreated polyethylene control samples. Thermally treated control samples will also be analysed so changes due to the presence of Lipiodol can be distinguished from changes due to thermal treatment.

2. Investigate the visibility of the radiopaque polyethylene components under the clinical set up:

    - To be achieved by first diffusing Lipiodol into unicompartmental mobile knee bearings to increase their radiopacity, and then assessing the visibility of the radiopaque polyethylene in standard radiographs and stereo-radiographs. Once the viability of medical imaging is confirmed, model-based Roentgen stereophotogrammetric analysis will be performed on the components and the precision and accuracy of the method quantified for polyethylene components.

3. Represent the distribution of Lipiodol within polyethylene after diffusion using numerical modelling, which can be successfully applied to different part geometries.

- To be achieved through the development of 1-dimensional, 2-dimensional, and 3-dimensional Fickian models, using finite elements. The model will be fitted to one set of geometrical data, and then validated on two different geometries to determine the accuracy of the model.

4. Understand the influence of treatment with iodised oil on the durability of the polyethylene:

    - To be achieved through the use of thermally accelerated ageing protocols to recreate the equivalent of five years of natural ageing. The tensile properties, oxidative stability and thermal properties (crystallinity, melting point) will be thoroughly investigated on the aged samples and compared with untreated controls, as well as vitamin E polyethylene. The leaching of Lipiodol will also be assessed over 8 weeks in simulated physiological conditions, and compared with vitamin E infused polyethylene.

Chapter 3

Characterisation of the physical, chemical and mechanical properties of a radiopaque polyethylene

3.1 Context

As explained in Chapter 1, there are set regulatory guidelines for the tests that need to be conducted on a new UHMWPE before considering it for clinical use. The radiopaque polyethylene should satisfy the safety requirements to ensure the patient safety and avoid any premature failure or damage. This chapter contains a published paper which investigated the chemical (crystallinity and oxidation), mechanical (tensile properties) and physical (radiopacity, melting temperature, gravimetric changes) properties of a radiopaque polyethylene using the corresponding ASTM or ISO standards. This introductory section covers the rationale behind the chosen examined properties and the experimental design.

3.2 Crystallinity

UHMWPE contains very long chains of polyethylene which are not static, and are able to rotate the carbon–carbon bond to arrange themselves in highly ordered sheet-like regions known as crystalline lamellae. These lamellae are embedded in disordered (amorphous) regions. The degree of crystallinity (the percentage of the volume that is crystalline) has a strong influence on the clinical performance of polyethylene. It is known that polyethylene degradation occurs primarily in the amorphous regions due to the high mobility of the chains [19], and based on this it is logical to hypothesise that if there were fewer amorphous regions that the degradation

would also reduce. In the late 1980's DePuy introduced a highly crystalline polyethylene under the trade name of Hylamer. Hylamer was advertised as "eternal polyethylene" as a result of its high crystallinity 70% (approximately 20% higher than conventional polyethylene) which it was assumed would reduce the risk of oxidative failure. This product was removed from the market as 84% of the cases had to undergo revision surgery within 4 years of implantation [20]. Clinical studies reported that the wear rate of Hylamer was 2.7 times higher than conventional polyethylene [21] and all the retrieved implants had severe evidence of cracking, delamination, and pitting. From the failure of Hylamer we can learn two things; firstly an increase in crystallinity can increase resistance to wear in the short term, and secondly that higher crystallinity can lead to increased material oxidation in the long-term. ASTM F2625 [22] outlines a standard method to calculate the percentage crystallinity in any polyethylene sample by using the theoretical heat of fusion of 100% crystalline polyethylene. The standard does not suggest a desired range of crystallinity, so it is common to use a successful polyethylene with a good clinical history as a control and to perform comparative analyses (such as has been performed in this work).

3.3 Oxidation

Oxidation of polyethylene can cause major complications for joint replacements, including delamination and pitting wear, osteolysis from wear particles, and implant fracture. Polyethylene oxidation requires two main reactants: a highly reactive species (most commonly free radicals) and oxygen. Free radicals are very likely to be found in UHMWPE as as result of the polymerisation process. Polyethylene is synthesised by Ziegler-Natta catalysis and polymerisation is via chain transfer, this increases the possibility of the formation of vinyl chain ends which are very reactive [111,23]. The second reactant is oxygen which is present in the air and also in biological environments, such as synovial fluid, which contain dissolved molecular oxygen. Oxygen is able to diffuse into the amorphous regions of polyethylene to react with the free radicals [27], hence polyethylene is always susceptible to oxidation. ASTM F2012-01 [25] describes the technique used to measure the oxidation index (OI) from Fourier transform infrared spectra. The oxidation index is a ratio of the carbonyl absorption peak and the peak due to the methylene stretch at 1369 cm^{-1}. ASTM F2012 specified that an OI of less than 1 is required for long-term medical applications. Manufacturers have introduced many different approaches to reduce the rate of oxidation, such as introducing cross-linking, performing sterilisation in inert gas rather than air, including additives such as vitamin E which are anti-oxidants, and using thermal treatments to reduce the quantity of free radicals within the polyethylene.

3.4 Mechanical properties

Polyethylene is a ductile polymer and the tensile stress-strain curve can provide a wealth of information that directly relates to the clinical performance of a polyethylene joint replacement bearing material. Tensile testing is the most common test conducted on UHMWPE, so there

is plenty of comparative data available. Both ISO[28] and ASTM[29] provided a standard method to examine the tensile properties of polyethylene.

3.4.1 Elastic modulus

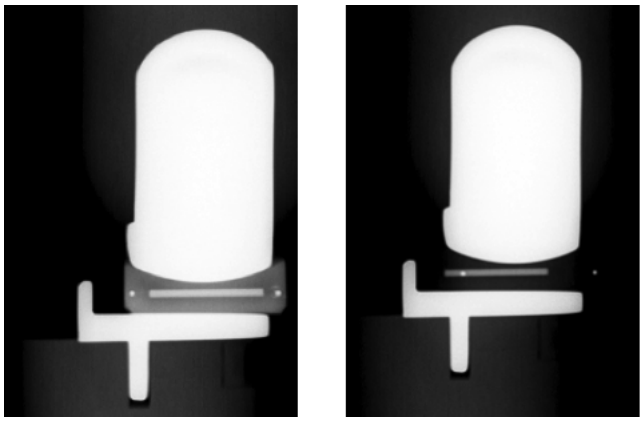
The elastic modulus (E) of a material represents its material rigidity and stiffness[32]. Orthopaedic bearings are subjected to elongation, bending and compression, as a result of the constant and cyclic physiological loading. A polyethylene with a very high elastic modulus, such as one with a high degree of cross-linking, can have very good wear properties; however, a similar elastic modulus might also be found for a standard polyethylene part which has undergone oxidation and is very brittle with low wear resistance. The elastic modulus of Hylamer was twice as high as GUR 415, but as explained Hylamer production was discontinued due to a high clinical wear rate[21]. Consequently the elastic modulus needs to be considered alongside other material information to fully understand what it represents. A very low elastic modulus can indicate the polyethylene will have a high rate of creep[31]. Polyethylene creep can lead to dimensional changes and implant designs which are reliant on tight tolerances (such as press-fit) it can be detrimental to implant function. Creep can also compound measurements of polyethylene wear; as polyethylene linear wear is calculated based on distance between two metallic parts and so in reality linear wear is a combination of material wear and creep[33].

3.4.2 0.2% Yield strength

When polyethylene is loaded below the yield strength, it is able to withstand load under tension without any irreversible deformation (assuming there is no material creep). The yield point of polyethylene has been used in many theoretical and analytical models to understand the mechanism of fatigue and wear of polyethylene components[35,36,37]. A polyethylene with a high yield strength is also associated with better crack-resistance properties[32]. From a design perspective, the yield strength of ductile materials for medical implants plays an important role in the material selection[32].

3.4.3 Ultimate tensile strength

The ultimate tensile strength (UTS) of polyethylene is known to be a function of processing and resin. From an implant perspective, fracture of polyethylene components can occur but it is rarely due to the material reaching its UTS and is more likely to be due to fatigue failure of the material. Nevertheless, it is important to quantify the UTS because it is linked to fatigue strength and the fracture toughness of polyethylene. Due to the high ductility of polyethylene materials, it is experimentally difficult to accurately calculate the fracture toughness of polyethylene, but studies have shown there is a linear relationship between the ultimate strength and the fracture toughness so it is possible to indirectly infer the fracture toughness from the UTS[38]. UTS is also a simple and relatively reproducible measure and hence is useful for making comparisons between different polyethylenes[32].



a **b**

Figure 3-1: a) The amount of overhanging of the bearing (size 4) can be identified directly from a radiograph due to the visibility of the bearing b) The overhanging can be confirmed from theradiographic markers, but the amount of overhang is harder to quantify.

3.4.4 Elongation at failure

The percentage elongation at failure identifies the amount of strain that the tensile test sample can withstand before fracture. Similar to UTS, it is unlikely that a polyethylene joint replacement bearing will be exposed to sufficient tensile stresses for a component to reach tensile failure in a single loading step, but the percentage elongation gives useful insight into the overall ductility of the material, which relates to creep and fracture resistance[32]. For instance, studies have demonstrated that it is possible to use the elongation at failure to predict the crack propagation behaviour of semi-crystalline polymers such as polyethylene during monotonic loading[37].

Overall, the tensile properties of polyethylene (elastic modulus, 0.2% yield strength, and UTS) play an important role in the long-term performance of the material *in vivo* and can be used, indirectly, to predict the likelihood of some common failures mechanisms including such as wear, fracture and fatigue.

3.5 Radiopacity

Currently, radiographic markers are used to identify the position of a polyethylene bearing, however, the information collected from the radiographic markers cannot be quantified. For example, Figure 3-1 shows the radiographs of a dislocated polyethylene bearing. The dislocation can be identified from the radiographic markers however, the radiopaque polyethylene bearing provides more information.

The level of radiopacity is correlated to the Lipiodol content which is location dependent and is inversely proportional to the distance from the diffusion surface. In this study the radiopacity was reported in two ways, bulk radiopacity or surface radiopacity. Analysis of the CT data was performed using Simpleware ScanIP (Synopsys, Inc., Exeter, UK, release version 2017). The gray-scale profile of each slice was measured and converted to Hounsfield units. The

bulk radiopacity was defined as the radiopacity of the entire length of the slice (Figure 3-2a) and the surface radiopacity was defined as the radiopacity of the first 2 mm below the surface (Figure 3-2b).

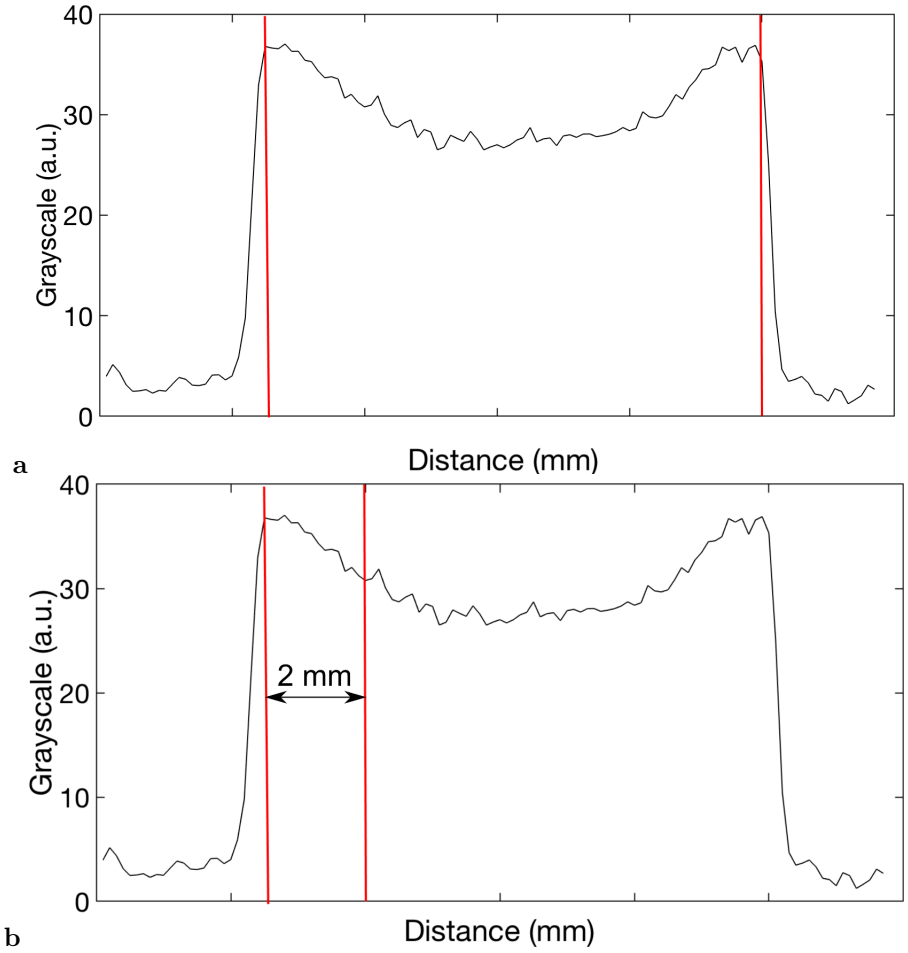


Figure 3-2: a) The bulk radiopacity of the samples was considered as the radiopacity between two edges of the samples and b) the surface radiopacity of the samples was considered as the gray-scale of first 2 mm below the sample surface.

From a clinical point of view both surface radiopacity and the bulk radiopacity can provide useful informations. For a single source X-ray many general complications can be identified from the overall radiopacity (Figure 3-1), however, more detailed information can be calculated from the surface radiopacity. For example wear of polyethylene bearing is a major complication and a common way to calculate the wear is by measuring the distance between two metallic components. For a radiopaque polyethylene, the wear can also be measured from the two outer surfaces of radiopaque polyethylene and and factors such as creep or edge loading could potentially be distinguished from the wear result like creep or edge loading do not affect the results. Later in this thesis, the importance of surface radiopacity will be explained for the

Figure 3-3: Photograph of the test samples after immersion in Lipiodol for 24 hours at 125°C, illustrating a colour change to brown and significant deformation of samples.

RSA measurements.

3.6 Experimental rational

As explained in Chapter 2, an elevated temperature is required to facilitate the diffusion of oil into polyethylene, to achieve an adequate amount of oil within a reasonable time frame. The thermal treatment conditions chosen for investigation in the paper within this chapter were selected based on results from a preliminary analysis performed on a wider range of thermal conditions (Appendix A). The study used a range of treatment temperatures from 85 to 125°C to diffuse different oily fluids (cis-9, cis-12-octadecadienoic acid and Lipiodol) into polyethylene samples. The result of this preliminary study showed significant thermal oxidation (OI>1) in the samples treated at 125°C. The samples were also significantly deformed as a result of swelling from oil-absorption (Figure 3-3) reducing the accuracy of any tensile tests[227]. Based on these results a treatment temperature range between 85 and 115°C was chosen for further investigation in the study presented in this chapter.

This paper presented in next section investigated the critical mechanical, physical and chemical properties of radiopaque polyethylene and compared it with standard polyethylene. The paper can be accessed at the following DOI: https://doi.org/10.1177/0885328220922809.

Appendix 6B: Statement of Authorship

This declaration concerns the article entitled:			
Characterisation of the physical, chemical and mechanical properties of a radiopaque polyethylene			
Publication status (tick one) **Draft manuscript** [ ] **Submitted** [ ] **In review** [ ] **Accepted** [ ] **Published** [x]			
Publication details (reference)	Zaribaf, F. P., Gill, H. S., & Pegg, E. C. Journal of Biomaterials Applications (2020). DOI: 10.1177/0885328220922809		
Copyright status (tick the appropriate statement) I hold the copyright for this material [ ] Copyright is retained by the publisher, but I have been given permission to replicate the material here [x]			
Candidate's contribution to the paper (provide details, and also indicate as a percentage)	The candidate considerably contributed to the The candidate contributed to the "**Formulation of ideas**", alongside the co-authors The candidate considerably contributed to the "**Design of methodology**": The candidate designed the methodology based on the knowledge available in the literature and the co-authors revised the proposed methodology and proposed amendments to improve the design The candidate conducted the "**experimental work**" under the supervision of Dr Elise Pegg The candidate considerably contributed to the "**presentation of data in journal format**": The candidate drafted the original manuscripts which has been revised by all the co-authors. Dr Elise Pegg significantly contributed to improve the quality of the manuscript and assisted with data visualisation.		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	F.Zaribaf	**Date**	27/11/2020

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Characterisation of the physical, chemical and mechanical properties of a radiopaque polyethylene

Fedra P Zaribaf, Harinderjit S Gill and Elise C Pegg

Abstract

Ultra-high molecular weight polyethylene has a low X-ray attenuation, hence, the performance of the polyethylene implants used for joint replacements cannot be directly investigated using X-ray-based imaging techniques. In this study, the X-ray attenuation of polyethylene was increased by diffusing an FDA-approved oil-based contrast agent (Lipiodol ultra fluid) into the surface of the samples, and the suitability of this novel radiopaque ultra-high molecular weight polyethylene for clinical applications was examined. Different levels of radiopacity were created by controlling the diffusion parameters, and the level of radiopacity was quantified from computed tomography scans and reported in Hounsfield units. The physical, chemical and tensile properties of the radiopaque ultra-high molecular weight polyethylene were examined and compared to untreated and thermally treated controls. The results of this study confirmed that for the samples treated at 115°C or less the diffusion of the contrast agent did not significantly alter the crystallinity ($p = 0.7$) or melting point ($p = 0.4$) of the polyethylene. Concomitantly, the tensile properties were not significantly different from the control samples ($p > 0.05$ for all properties). In conclusion, the radiopaque ultra-high molecular weight polyethylene treated for less than 18 h at a temperature of 115°C or below is a promising candidate for joint replacement applications as it can be identified in a standard X-ray while retaining the tensile properties of clinically used radiolucent ultra-high molecular weight polyethylene.

Keywords

Polyethylene, radiopaque, tensile properties, imaging, joint replacement

Introduction

Ultra-high molecular weight polyethylene (UHMWPE) is the articulating material used in the majority of joint arthroplasties. Clinical studies on joint replacements have showed that on average the revision rate for hip and knee replacements at 14 years is 6%,[1] but despite the overall success of the procedure, the polyethylene bearing can dislocate (3.3% of partial knee replacement failures), fracture (2.2%) and severely wear (4%).[2] Informed post-operative follow-up and evaluation of the clinical performance of a polyethylene part could lead to early diagnosis of such failures, which would benefit patient outcomes. Currently, the early diagnosis of failure, particularly of all-polyethylene components, can be challenging as the UHMWPE part cannot be identified on standard radiographs.[3]

There are a few ways to monitor the position and condition of the polyethylene bearing from post-operative radiographs, but none of these collects the information directly from the polyethylene implant. Some polyethylene prostheses contain radiopaque metallic markers, which are positioned within the bearing, however, the radiopaque marker can increase the risk of polyethylene fracture.[4] Radiopaque markers can aid the identification of some complications such as dislocation and fracture, but not issues such as wear or creep. *In-vivo* wear progression of polyethylene bearings is often inferred from the metallic parts in contact with the polyethylene components.[5] For example, in hip replacements the wear can be calculated based on the total penetration of the femoral head into the acetabular cup on radiographs.[6,7] Similarly, in knee

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replacements, to examine the wear, the minimum distance between the femoral condyles and the tibial plateau can be measured.[8] A major limitation of relying on the metallic components to indirectly assess the polyethylene state, is that these measurements require a weight-bearing radiograph, which is often not used clinically, and the calculated wear also includes creep and bearing compression.[9] Furthermore, mild and moderate wear are often difficult to identify as the measurements are often from a single-source X-ray image. The interpretation of a single source radiograph is dependent on imaging angle and the patient position,[10] double source radiographs are also an option but relatively few hospitals are equipped with stereo-imaging systems.

The current study investigates the possibility of using a novel radiopaque UHMWPE as an alternative. We hypothesised that the radiopacity can be increased by incorporating an oil-based contrast agent (Lipiodol ultra fluid) into UHMWPE. Due to the oily nature of the fluid, the contrast agent can be diffused into the polyethylene part using an elevated temperature.

Lipiodol ultra fluid (hereafter Lipiodol), also known as ethiodised oil, is an iodised-poppy seed oil which is a pale yellow oily fluid. The fluid changes colour when it is thermally treated. In Lipiodol, the carbon–carbon double bond is saturated using iodine, hence the oil can be detected with a standard X-ray. This contrast agent has FDA-approval and is often used in diagnostic and interventional radiography.[11–13] The density of Lipiodol is 1.28 g/cm and 1 ml of solution contains 480 mg of iodine (37% w/w).[12] The fluid only contains naturally occurring unsaturated fatty acids.[12] The predominant fatty acid in poppy seed oil (the precursor for Lipiodol) is a triglyceride, the fluid also contains other lipophilic ingredients such as Linoleic acid side chains (60%–70%), tocopherols and α-tocopherol (vitamin E).

When considering a new polyethylene, patient safety is paramount, so it is essential that the properties of the new polyethylene are thoroughly investigated to ensure it is equivalent to currently used polyethylene. Other oil-based fluids (e.g. vitamin E) have been incorporated into medical grade UHMWPE and used clinically. The presence of vitamin E led to no significant alteration in the tensile properties of the polymer and improved aging properties, but an increased ductility and creep has been reported[14,15] and there is potential for similar observations with Lipiodol-infused polyethylene. For vitamin E polyethylene these effects have been mitigated through optimised diffusion protocols including a homogenisation step which leads to more even distribution of vitamin E throughout the part, and γ-irradiation to increase crosslinks in the polymer.[16]

The aim of the current study was to examine the effect of Lipiodol on the physical (dimensional and thermal), chemical (crystallinity and oxidation) and mechanical (tensile) behaviour of medical grade UHMWPE (GUR 1050).

Materials and methods

The experiments were designed to answer the following questions:

- Do the treatment conditions (temperature and time) correlate with Lipiodol uptake?
- Does the Lipiodol treatment lead to any alteration in the physical properties (weight, colour, dimension melting point, or radiopacity)?
- Does the Lipiodol treatment significantly change the chemical properties (crystallinity or oxidation)?
- Does the Lipiodol treatment lead to any changes in the tensile properties (modulus, elongation at break, ultimate tensile strength)?

Sample preparation

Tensile test specimens were machined based on ISO-572 Annex A, type 1AB.[17] All the samples were made from un-irradiated medical grade UHMWPE manufactured from GUR 1050 moulded UHMWPE sheets 160 mm square and 4 mm thick from (Celanese, Oberhausen, Germany). A sheet of GUR 1050 was also cut to small cuboids of $10 \times 15 \times 4$ mm, for oxidation and crystallinity analysis. Table 1 summarises the type of samples used for each experiment (five repeats for all tests).

Table 1. The following experiments were conducted to examine the physical, chemical and mechanical properties of radiopaque UHMWPE.

Test type	Samples type	Investigated properties
Tensile testing	ISO-572 Annex A 1AB tensile	Tensile properties
Thermal properties (DSC)	Cuboid 10 × 10×4 mm	Cystallinity and melting point
Oxidation properties (FTIR)	Cuboid 10 × 10×4 mm	Oxidation
Radiopacity (CT scan)	Cuboid 10 × 10×4 mm and ISO 1AB tensile	Lipiodol uptake
Gravimetric changes	ISO-572 Annex A 1AB tensile	Lipiodol uptake

Lipiodol diffusion

Samples were immersed into 25 ml of Lipiodol for either 12, 18 or 24 h and a range of elevated temperatures (from 85°C to 115°C) was applied to facilitate the diffusion. Preliminary results[3] showed temperatures above 120°C caused oxidation and changed the crystallinity of the polyethylene. Therefore, in this study, diffusion temperatures were kept below 120°C. All treatment temperatures were therefore also below the melting point of polyethylene (135°C ± 2°C) so preserved the crystalline content.[18] The different combinations of treatment temperatures and times examined are summarised in Table 2. After treatment, the samples were allowed to cool down to ambient temperature and wiped with a lint-free tissue to remove any excess Lipiodol from the surface.

Samples held at 105°C for 18 h but not immersed in Lipiodol were used as thermal controls to assess the impact of the Lipiodol treatment independently of temperature. For the tensile tests, untreated control samples without thermal treatment were also tested, representing virgin uncrosslinked polyethylene.

Table 2. Treatment conditions and the number (n) of repeats used for each study.

Time (h)	Temperature (°C)		
	85	105	115
12		$n=5$	
18	$n=5$	$n=5$	$n=5$
24		$n=5$	

Determination of Lipiodol content from gravimetric change

The weight of all samples was measured using a digital scale (Mettler Toledo XP205, OH, USA) before and after the treatment. The effect of thermal treatment on the weight of the samples was also recorded. This information was used to calculate the percentage of gravimetric change in the samples due to the absorption of Lipiodol.

Determination of Lipiodol content using FTIR

A thin slice (approximately 200 μm thick) was sectioned using a sledge microtome (MSW-106SM, India) from the surface of the samples. A Thermo Scientific spectrometer (Magna 560 IR, Nicolet, MA, USA) was used to obtain the Fourier-transform infrared (FTIR) spectra in transmission mode. An average of 32 scans was taken for each section from 4000 to 600 cm^{-1}. The Lipiodol concentration was calculated from the areas under the Lipiodol absorbance peak at 1728 cm^{-1} (Figure 1). This peak was assigned to Lipiodol as it was present in all the spectra of pure and diluted solutions of Lipiodol. Peaks between 1730 and 1750 cm^{-1} are due to the ester group (Lipiodol is the ethyl ester of poppy seed oil (Table 3). The exact position of the peak depends on the functional groups attached to the ester group. Lipiodol contains iodine, and the presence of an

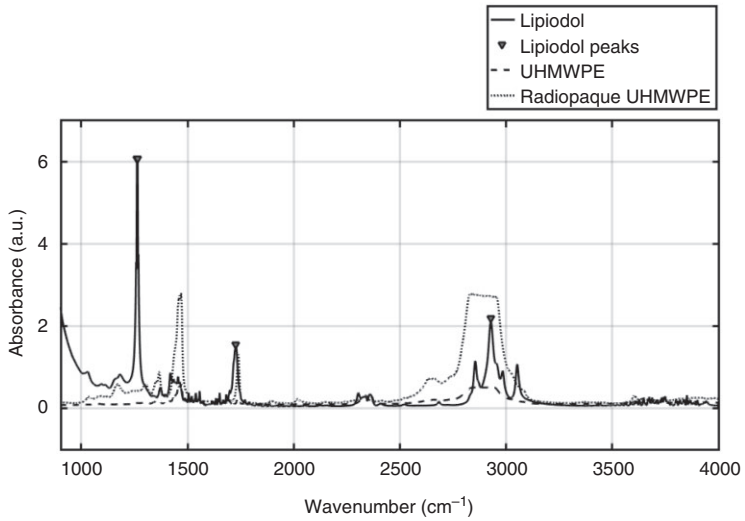

Figure 1. The FTIR spectra of pure Lipiodol, untreated UHMWPE and radiopaque UHMWPE. The peak located approximately at 1730 cm^{-1} indicates the ester group in Lipiodol; this peak can be identified in the Lipiodol and radiopaque UHMWPE spectra.

Table 3. Main bands identified in the FTIR spectrum of Lipiodol.

Peak (cm^{-1})	Functional group
1263[32]	Phenolic C–O (tocopherols), methyl ester, (C–O–C)
1730[33]	Ethyl ester (due to starching the carbonyl group)
2900[19]	Phythyl chains (tocopherols) symmetric (C–H)
3050[32]	v(C–H), v(=CH)

electronegative group can shift the peak by 15 cm^{-1}.[19] The area under the peaks was compared to the calibration curve made from the known solutions of Lipiodol, and the concentration was calculated using Beer-Lambert's law.[19]

Radiopacity measurements

Each sample was imaged using a μCT scanner (X Tec, XT H 225 ST, Nikon Metrology UK Ltd, Derby, UK), scanning protocols were the same for all samples (162 kV, resolution 0.2 mm). Analysis of the computed tomography (CT) data was performed using Simpleware ScanIP (Version 2017, Synopsys, Inc., Exeter, UK). Water, air and untreated polyethylene were used for calibration to calculate the Hounsfield units (HU).[20]

Melting point and crystallinity measurement

Differential scanning calorimetry (DSC) was used to determine the melting point and the degree of crystallinity of UHMWPE ($n = 5$). Approximately 2.0 mg of each sample was taken from the outer surface of the samples and then was analysed (DSC 250, TA Instruments, DE, USA). The pan was crimped with an aluminium cover. The testing was conducted from 20°C to 180°C at a heat flow of rate 10°C/min under a nitrogen purge. TA Universal Software (Version 4.5) was used to analyse the data and calculate the degree of crystallinity using the following steps:

- The endothermic peak was integrated from 50°C to 160°C to find the enthalpy of fusion of the sample.
- The enthalpy of fusion obtained was then normalised with the heat of fusion of pure UHMWPE (289 J/g).[21]

Determination of oxidation using FTIR

The FTIR spectra obtained from the polyethylene slices were also used to calculate the oxidation index according to ASTM F2102.[22] There are different peaks, which signify the oxidative degradation such as the transvinylene peak at 965 cm^{-1} or carbonyl absorption peak at 1720 cm^{-1}. The oxidation index (OI) is the area under the carbonyl absorption peak divided against the peak due to the methyl stretch at 1396 cm^{-1}.[22] The standard method of calculating the oxidation index requires using the carbonyl peak which is located around the same area as the peak representing the Lipiodol. Hence, we were unable to calculate the oxidation index of samples but to ensure there was no significant oxidation reaction, each spectrum was checked for other oxidation by-products (transvinylene) at 950 cm^{-1}.

Tensile mechanical testing

Tensile tests were conducted at room temperature (~20°C) in accordance with ISO-527[17] using an electromechanical test machine (Instron 5965) at a rate of 50 mm/min. The tests were carried out with virgin UHMWPE, thermally treated UHMWPE and Lipiodol treated UHMWPE. Five specimens per condition were tested to obtain tensile modulus (E), 0.2% yield strain, ultimate tensile strength (UTS) and elongation at failure. The raw data were processed by a custom Matlab code (R2012a, Nattick, MA, USA) to extract tensile properties. The calculations were conducted as specified in the standards. The initial displacement (first 10 s, equivalent of approximately 0.3% strain) data was measured using a high-speed camera (DFK 33UX290, Imagingsource, Germany).

Statistical analysis

Sample groups were compared using a Kruskal–Wallis test and multiple pairwise comparisons where applicable, a p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS software (Version 25, IBM, New York, USA).

Results

The physical, chemical, and tensile properties of the radiopaque UHMWPE were examined and compared to untreated controls to investigate the suitability of the radiopaque polyethylene for clinical applications.

Gravimetric change and infrared spectroscopy were used to estimate the Lipiodol intake (Table 4). The Lipiodol treated samples significantly increased in weight (up to 30%), whereas the weight change of the samples only treated thermally was as low as 0.5%. The Lipiodol concentration measured using FTIR (Figure 1) showed that there was a linear correlation between the Lipiodol concentration and weight change, with a Pearson's correlation coefficient of 0.983. The lowest amount of Lipiodol detected in the treated samples by FTIR was 0.3% v/v, which was for the samples treated at 85°C, and there was a power relationship between temperature and Lipiodol concentration. A significant alteration was also observed in the dimensions (up to 27% volume increase) of the samples

Table 4. Influence of Lipiodol diffusion temperature on Lipiodol uptake and physical properties (mean ± SD).

Temperature (°C)	Volume change (%)	Weight change (%)	Lipiodol conc. (%v/v)
85	1.6 ± 0.4	2.0 ± 1.1	0.9 ± 0.4
105	6.5 ± 1.5	4.7 ± 1.0	5.8 ± 1.9
115	26.5 ± 3.1	29.9 ± 3.5	19.8 ± 3.6
105-Control	0.1 ± 1.7	–	0.3 ± 2.0

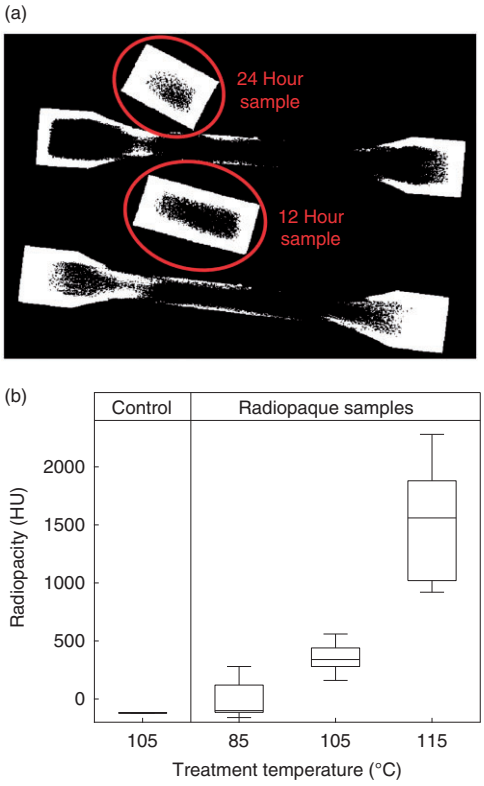

Figure 2. Treatment with Lipiodol increased the radiopacity of the samples and this was dependent on treatment temperature and time, as demonstrated by (a) a CT scan slice through the centre of UHMWPE samples treated at 105°C for 12 and 24 h; the white regions indicate the presence of Lipiodol and (b) the correlation between Hounsfield unit and treatment temperature.

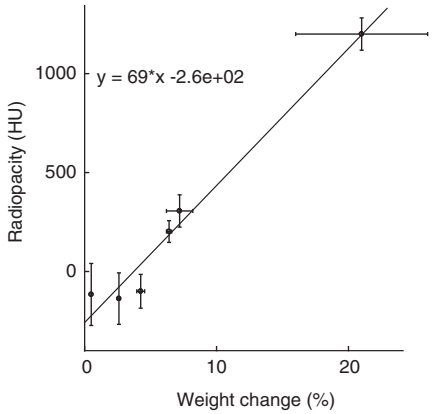

Figure 3. The level of radiopacity linearly correlated with gravimetric changes ($R^2 = 0.921$).

(Table 4 and Figure 4), and the colour of the samples changed from white to dark yellow or dark grey, depending on the treatment temperature and duration.

The radiopacity level was increased by the treatment and was directly correlated with Lipiodol intake (Figures 2 and 3). X-ray attenuation can be directly correlated with the mass thickness (mass per area), and a linear relationship was seen between the radiopacity level and gravimetric change (Figure 3, Pearson's correlation coefficient of 0.921).

The DSC results found that there was no significant change in the melting point ($p = 0.4$) or the crystallinity ($p = 0.08$) of the radiopaque polyethylene ($p = 0.4$) (Figure 4) indicating no alteration in the thermal properties of polyethylene after the Lipiodol treatment.

The study also investigated the oxidative stability of the samples after the treatment. The FTIR spectra showed the treatment did not cause oxidation in the samples within 24 h of the treatment. The oxidation index of thermally treated samples was between 0.2 and 0.4. Based on the current standard[22] oxidation index less than one confirms that the polyethylene is suitable for clinical applications.

The effect of time and temperature on the tensile properties of the radiopaque polyethylene was investigated. The modulus and the 0.2% yield strain of the samples treated at 115°C for 18 h were significantly lower than the untreated samples (modulus: $p = 0.01$, yield: $p = 0.04$), and there was a reducing trend in the modulus of the samples as the treatment temperature increased (Figure 5(c)). The correlation coefficient of the line was −0.9, which suggests a negative monotonic correlation between the modulus of the samples and the concentration of Lipiodol. The elongation at failure increased with temperature at a rate average of 30% (Figure 5(g)). The effect of the treatment duration on the tensile properties was also examined. As Figure 5(f)

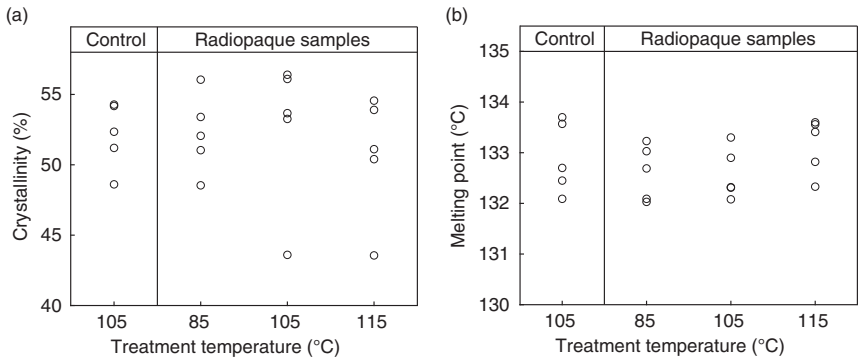

Figure 4. No significant change was observed in (a) the crystallinity ($p = 0.08$) or b) the melting point ($p = 0.4$) of the treated samples compared to the untreated controls.

shows, the ultimate tensile strength of the samples increased significantly at 24 h ($p = 0.046$). The other tensile properties of polyethylene (elongation at failure $p = 0.052$, yield $p = 0.15$ and modulus $p = 0.09$) of the samples were not affected significantly by the treatment duration.

Discussion

This study investigated a novel UHMWPE for medical applications, which has a significantly higher radiopacity than conventional polyethylene. The increased radiopacity was due to the presence of an FDA approved radio-contrast agent called Lipiodol, which is an iodised oil. Thermal treatment is necessary for the diffusion and to obtain enough Lipiodol throughout a component to be able to identify the part in a radiograph. However, the thermal treatment can potentially alter the part dimensions, crystallinity and tensile properties.[23] Hence, to ensure patient safety, it is crucial to prevent any significant alteration in the material and mechanical properties of this novel radiopaque polyethylene. This study fully characterised the physical, chemical and mechanical properties of the novel UHMWPE. It was important to distinguish between changes due to temperature and those due to the Lipiodol treatment, so heat treated control samples were used.

The degree of the crystallinity is one of the most important properties of UHMWPE as it directly influences the tensile properties of the part. The thermal treatment can alter the crystallinity,[23] a reduction in the degree of crystallinity causes a higher risk of oxidation and oxidative failure, while an increase of degree of crystallinity increases the brittleness of the polyethylene, and makes the polyethylene part less suitable for load-bearing applications.[24] The results of this study found that none of the treatment conditions altered the studied thermal properties of UHMWPE. This agrees with studies on vitamin E incorporated UHMWPE (the only other example of an oil-infused medical polyethylene) which showed no difference in crystallinity after treatment.[25]

However, the treatment with Lipiodol caused an overall increase in the ductility of polyethylene which was identified by a reduction in the modulus and an increase in the region of ductile deformation in the stress–strain curve (increased elongation at break).[26] This alteration was not seen in the control samples treated only with temperature, indicating that the Lipiodol is cause of these alterations. Many studies have correlated changes in ductility to changes in crystallinity, recrystallisation or the molecular weight of the polymer,[21,27] however, as mentioned, there was no evidence of alteration of these properties. A similar plasticising effect has been reported for vitamin E polyethylene, and has been explained by alterations in the crystal structure of polyethylene in the presence of an oil. Oral et al.[28] reported that the pressure-temperature phase diagram of polyethylene is altered by the presence of vitamin E.[28] The crystalline regions formed in the hexagonal phase are less dense than those in orthogonal phase, this allows greater mobility and diffusion of chains in a specific direction leading to changes in the crystalline structure, and hence the mechanical properties without changing the degree of crystallinity. Oral et al. demonstrated that this effect can be mitigated through irradiation-induced crosslinking,[29] a similar approach may be successful for the radiopaque polyethylene.

The ultimate tensile strength (UTS) of polyethylene was found to be unaffected by the treatment temperature and duration. This is encouraging as it has been proven that a reduction in UTS indicates the reduction

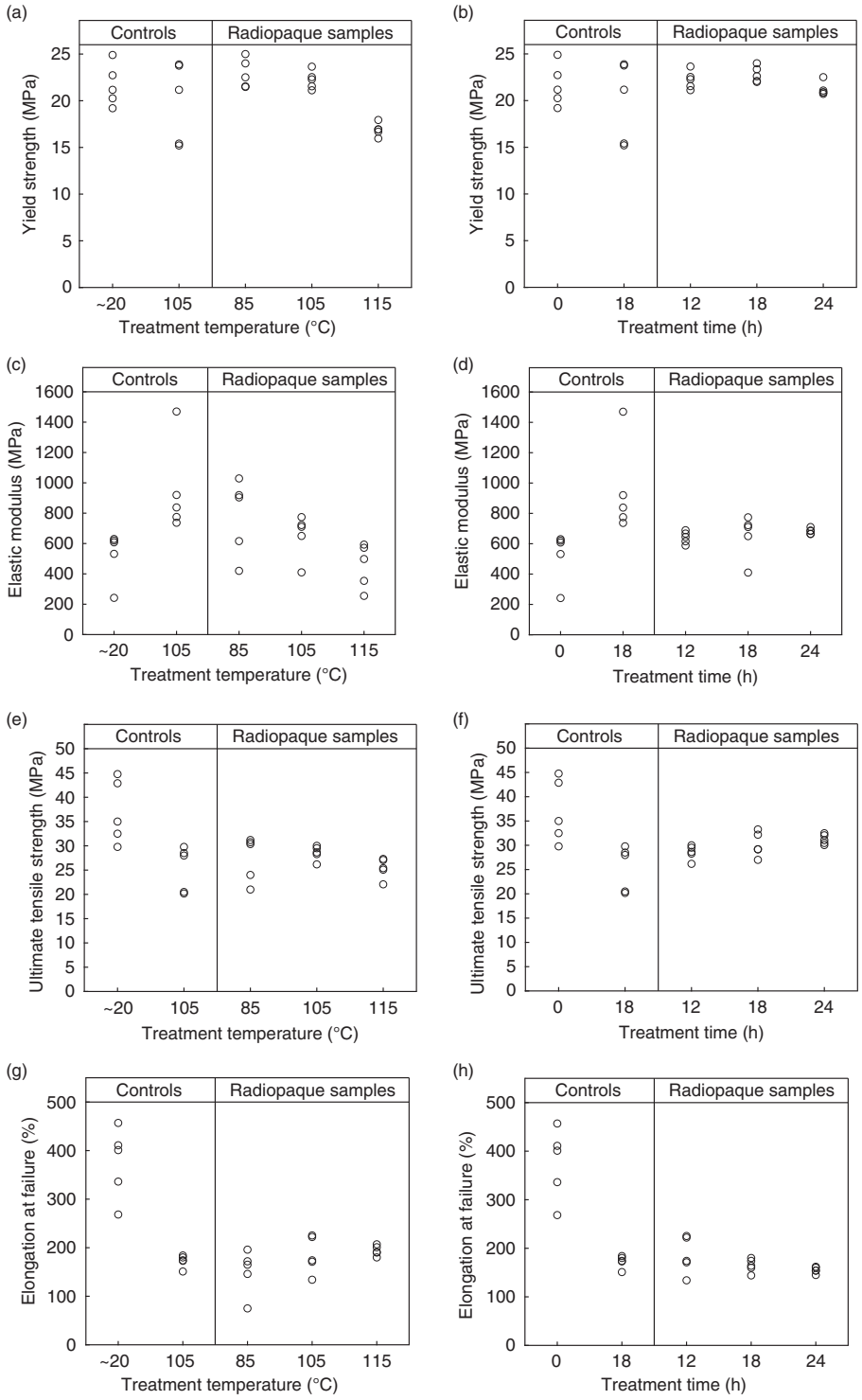

Figure 5. The temperature of the treatment changed the modulus at 115°C ($p = 0.013$) and yield strength ($p = 0.04$) but the ultimate tensile strength (UTS) ($p = 0.24$) and elongation at failure ($p = 0.1$) of the samples were not statistically different. The treatment duration, however, changed the material properties only when the duration exceeded 24 h (modulus ($p = 0.093$), UTS ($p = 0.02$)). No changes were observed in the yield ($p = 0.159$) and elongation at failure ($p = 0.2$).

of the fatigue resistance.[26] However, the fatigue properties of this radiopaque polyethylene still need to be investigated and is planned as part of future work.

The mechanical test results had unusually high variation in properties such as UTS and yield, this was noticable for the untreated control samples as well as the treated radiopaque samples. A possible explanation is the anisotropic properties resulting from compression moulding, the samples were cut from a small moulded sheet (160×160 mm) and greater crystalline alignment will occur at the edges[30] causing inhomogeneity in the sample set. Although the variability is high, the results for the control samples without thermal treatment are consistent with that published for uncrosslinked UHMWPE.[31]

It was also observed that there was a significant dimensional change in the Lipiodol treated samples. Some of this change could be attributed to the release of residual stresses from the previous manufacturing steps (e.g. moulding), but the samples treated only with temperature showed 0.1% increase indicating dimensional changes from residual stress were comparatively minor. One possibility is that the majority of the swelling observed is due to the accumulation of Lipiodol in the surface of the samples. In the similar cases (diffusion of vitamin E) an extra homogenisation process was added to allow the oil to move from the surface throughout the sample which reduces a small part of the dimensional change.[29] Provided this expansion is known, and it can be taken into account during the design of an implant or additional machining stage added after treatment to meet required tolerances.

Finally, we acknowledge the limitations of this work. The results of this study cannot be directly compared with other studies. This is because the mechanical properties of polyethylene are controlled by molecular weight, crystal alignment and the uniformity of the resin powder during the consolidation,[27] hence changes in the mechanical properties cannot be immediately attributed to any alteration in material structure caused by the contrast agent.[21] Furthermore, microdogbone (ISO-572-Annex A) samples were used for this study and some studies have suggested that smaller test samples can lead to size-dependent properties.

Conclusion

This study has demonstrated that it is possible to significantly increase the radiopacity of medical grade polyethylene through the diffusion of iodised oil, enabling improved implant follow-up of joint replacement complications such as dislocation and wear. The optimal treatment conditions were when the polyethylene was immersed in iodised oil at 105°C for 18 h, which resulted in a radiopacity of approximately 500 HU with no significant change in crystallinity, melting point, tensile strength, yield, elongation at failure or oxidation, when compared with standard untreated polyethylene. However, the iodised oil caused a plasticising effect at temperatures and times in excess of the optimum conditions (increased elongation and decreased modulus) highlighting the importance of careful selection of treatment conditions, it may be possible to mitigate these effects through crosslinking. In summary, the radiopaque polyethylene has shown promising mechanical properties for joint replacement applications. To further assess the safety of this novel material for medical applications, future work will examine the influence of longer-term loading (fatigue and creep) and aging of the polyethylene in in vivo conditions.

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3.7 Summary

As explained in Chapter 2, one of the primary objectives of this study was to understand the influence of Lipiodol treatment on the critical properties of polyethylene, including; the crystallinity, melting point and tensile properties, all of which indicate the potential of the material for long–term clinical application. The key findings of this study are summarised below.

- The Lipiodol intake directly correlated with the treatment temperature (Pearson's correlation coefficient of 0.921). This thermal sensitivity of the diffusion is not unexpected, but it demonstrates how the treatment condition can be used to tailor the bulk radiopacity if desired. Different implant applications may have different radiopacity requirements; for instance, this thesis focuses on joint replacement applications where due to the surrounding metallic components it is necessary for the bearing to have a radiopacity of a similar magnitude so it is visible, and so requires a fairly high treatment temperature. For an application such as suture repair of soft tissue a much lower radiopacity may be preferred to enable better visualisation of the surrounding tissue and so a more moderate treatment temperature might be chosen.

- The presence of Lipiodol within the polyethylene did not alter the crystallinity or the melting point, at any of the treatment conditions examined. As highlighted in Section 3.2 the crystallinity influences long-term properties such as oxidation and wear. That the crystallinity was equivalent to that of untreated polyethylene suggests the long–term performance would also be comparable.

- The results found an inverse correlation between the modulus of polyethylene and Lipiodol intake, which was hypothesised to be due to the plasticising effect of Lipiodol which led to an increase in the viscous flow of the chains. As outlined in Section 3.4.1 a reduced elastic modulus of polyethylene can be associated with increased creep and potentially reduced wear resistance of a joint replacement bearing. There is a balance to be achieved between the necessary radiopacity and the material properties of the polyethylene. The same compromise was necessary for vitamin E polyethylenes, which used cross-linking to mitigate the effects on modulus; cross-linking was not investigated in this work but is a further avenue worth exploring. The difference in modulus between the untreated control samples and the Lipiodol treated samples only became statistically significant at 115°C; so this study recommended the optimal Lipiodol diffusion conditions of 105°C for 18 hours. In this safe window of treatment, no significant change in the modulus was observed.

- Overall, radiopaque polyethylene when treated at 105°C for 18 hours showed promising properties for long–term joint replacement applications, with crystallinity, melting point, and mechanical properties comparable to standard medical grade polyethylene. The treatment successfully increased the radiopacity of polyethylene to approximately 500 HU which is lower than metallic components but close to that of bone.

Chapter 4

Contrast enhancement makes model-based Roentgen stereophotogrammetric analysis possible for polyethylene implants

4.1 Context

Clinical post-market surveillance is the practice of monoitiring the performance and saftey of medical devices after it has been realsed on the market and it is an obligotory requirement by many regulatories bodies like (FDA, MHRA, EU regulation). This is because it is extremely important to ensure medical device design safety and performance. Introducing a new device to the market with insufficient clinical testing can have a catastrophic outcome. For example in 1991, 3M Health Care Ltd. (Loughborough, United Kingdom) launched a new hip implant called the Capital hip which was a very low-cost design with promising *in-vitro* performance. Within six years, approximately 5000 patients were implanted with the Capital hip in 92 hospitals around Europe. Clinical studies showed a 20% failure rate at five years[42] and it was withdrawn from the market in 1997; if the faults with the design had been identified early on through effective post-market surveillance then the usage of the hip would not have been so widespread. Even today after twenty years, the disastrous failure of a new device is not uncommon (Articular Surface Replacement metal-on-metal hip arthroplasty); and this is in part because thorough clinical post-market surveillance takes a long time, it is costly, and requires a considerable number of patients for high quality data[43].

Model-based Roentgen Stereophotogrammetric Analysis (MBRSA) is a very accurate radiological technique, and is considered the gold standard post-market surveillance tool (ISO 16087:2013[30]) for an early clinical trial of a new metallic joint replacement implant. MBRSA quantifies migration of metallic implants to a sub-millimetre accuracy and can give an early-indication of wear rates. The high accuracy provides data of sufficient quality from only a small number of patients (thirty to forty) for a clinical trial[43]; this lowers the cost of the trial, the risk to the patients, and gives an indication of the performance of the implant in a much faster time frame. MBRSA analysis would typically be performed on radiographs taken within five days of the operation (weight-bearing images are recommended), at six months, one year and two years of the operation[28].

In the past 10 years there has been a renewed interest in all-polyethylene implants (such as the Monobloc cup from Mathys Orthopaedics). All-polyethylene components have a lower modulus, which means they transfer the load better to the underlying bone which reduces the likelihood of stress shielding. All–polyethylene components are also cheaper to produce[44] compared to traditional metal–backed components. Due to the limited X-ray visibility of polyethylene, currently it is not possible to use MBRSA for all–polyethylene implants.

The paper presented in this chapter investigated the potential of radiopaque polyethylene created through Lipiodol diffusion for MBRSA. The components were tested using a clinical set-up and a series of phantom-based experiments were conducted to investigate the feasibility of using MBRSA analysis for the radiopaque polyethylene material. All experimental work was performed at Leiden University Medical Centre (LUMC) in the Netherlands as part of a Santander Postgraduate Mobility Award 2–month placement.

Appendix B: Statement of Authorship

(An editable, Word version of this form is available here, on the Quality Assurance Code of Practice statements webpage).

Appendix B: Statement of Authorship

This declaration concerns the article entitled:			
Contrast enhancement makes Model-based Roentgen Stereophotogrammetric analysis possible for polyethylene implants.			
Publication status (tick one) **Draft manuscript** ☑ **Submitted** ☐ **In review** ☐ **Accepted** ☐ **Published** ☐			
Publication details (reference)	Fedra P, Zaribaf., Lennord A, Koster., Bart L, Kaptein,. Elise C Pegg. Harinderjit S. Gill.		
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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	The candidate contributed to / considerably contributed to / predominantly executed the… Formulation of ideas: 100% Design of methodology: 100% Experimental work: 100% Presentation of data in journal format: 100% Co-authors revised and feedback all the stages		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	F zaribaf	**Date**	21/june/2020

Contrast Enhancement makes Model-based Roentgen Stereophotogrammetric Analysis Possible for Polyethylene Implants

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Abstract

Model-based Roentgen Stereophotogrammetric Analysis (RSA) is able to measure migration of metallic prostheses with submillimeter accuracy. However, model-based RSA cannot be directly used for polymeric materials due to their limited X-ray attenuation. In this study the radiopacity of Ultra-High Molecular Weight Polyethylene (UHMWPE) prosthetic components were increased by diffusing an oil-based contrast agent into the surface of the samples. The feasibility of using this novel radiopaque UHMWPE for RSA studies was examined by measuring the precision and accuracy of the unicompartmental knee bearings. Radiopaque unicompartmental knee bearings were created with three different levels of surface radiopacity and model-based RSA performed. The results of this study confirmed it was possible to locate the radiopaque bearings in the stereo-radiographs using the model-based RSA with a 95% accuracy in the superio-inferior direction with a precision comparable to metallic parts for translational movements (0.03 to 0.50 mm). For rotational movements the precision was lower (0.1 to 3.0°). To determine the optimal level of radiopacity, the precision level of the system for all the radiopacity levels was calculated and compared; no significant difference was found in precision for the different levels of radiopacity (p=0.08). Overall, this study confirmed that contrast enhanced radiopaque polyethylene can be used for model-based RSA studies.

Keywords: Model-based RSA, Radiopaque UHMWPE, Unicompartmental Knee Bearing, Imaging

1. Introduction

Ultra-high molecular weight polyethylene (UHMWPE) has been widely used in joint replacement applications due to its strength and relatively low friction coefficient [1, 2]. Despite the high success rate of joint replacements (approximately 96% for knee replacements, between 15 to 20 years) [3] an UHMWPE implant has a limited lifespan and mechanical failure of the polyethylene bearing is not uncommon [4, 5]. For the younger and/or active patient, there is a higher mechanical demand on the implant, which increases the risk of wear and loosening [3] Some of the available designs such as the Oxford Partial Knee (Zimmer-Biomet, Bridgend, UK) with a mobile bearing are considered more suitable for younger active patients. Mobile bearings of this type aim to reduce the wear and loosening by increasing the surface area to reduce the contact stress and enhance the load distribution to the surrounding tissues [6]. However, edge-loading and contact-loss can occur between the articulating surfaces of the mobile knee during cyclically loaded motions like cycling and walking upstairs [7]. Edge loading increases the local stress hence increasing wear and the chance of premature failure. Contact loss can cause inaccuracies in quantification of wear. Other complications such as bearing dislocation, mal–alignment, fracture and overhanging can also occur, leading to an increased risk of failure [8, 7, 5]. Currently, none of the stated issues can be readily visualised in radiographs of polyethylene components due to the low X-ray attenuation of UHMWPE, which makes post-operative follow-up and direct imaging of the bearing challenging. We have developed a novel radiopaque polyethylene, visible on standard radiographs, in which the radiopacity of polyethylene is increased by diffusing an FDA approved oil-based contrast agent (Lipiodol Ultra-fluid [hereafter Lipiodol], Guerbert, France) into the surface of the polyethylene bearings (Figure 1) [9]. In Lipiodol, the carbon-carbon double bond is saturated with iodine so it can be detected on

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standard radiographs [10].

Currently, many mobile polyethylene prostheses contain metallic radiopaque markers, which are positioned within the bearing [11]. The radiographic markers provide information about the position of the polyethylene component. However, these markers cannot be used for model-based RSA studies. Additionally, the metallic radiographic markers can jeopardise the mechanical function of the bearing as they can lead to localised stress concentrations within the bearing [11]. Our novel radiopaque UHMWPE enables the direct imaging of the prosthesis both during and after the surgery, which would assist with early diagnosis of failure and identification of reported complications such as overhanging and contact-loss, and potentially early wear [12]. Our previous work has confirmed that the radiopaque polyethylene is a promising candidate for joint replacement. The tensile properties of the radiopaque polyethylene are comparable with standard UHMWPE which has been used clinically for more than six decades [13].

Roentgen Stereophotogrammetric Analysis (RSA) is a dual source X-ray imaging technique which can accurately determine the three dimensional positioning of an object [14, 15]. Conventional RSA requires tantalum beads to be embedded within the bone and attached to the implant. Model-based RSA (MBRSA) matches the projected contour of the implant with contour of the implant observed in the stereo-radiographs, thus negating the need for the beads but requiring components to be radiopaque [16, 17].

Currently, MBRSA is used for accurate measurement of the position and migration of metallic implants with respect to the surrounding bone and has a precision level as high as 0.06 mm for any translational movement in different directions [18]. MBRSA is recommended for post market surveillance of joint replacement designs, as it is able to accurately quantify *in vivo* rigid body kinematics. However, MBRSA cannot be directly used on polyethylene components due to their low X-ray attenuation and, there is currently no alternative technique to evaluate polyethylene implant motion *in vivo* with such a high degree of precision. This is a significant limitation, particularly for the evaluation of all-polyethylene implants.

The aim of this study was to investigate the feasibility of using the novel radiopaque polyethylene components for MBRSA analysis in a clinically relevant context. To achieve this aim, the precision and accuracy of the system were thoroughly investigated by a series of phantom based experiments. Precision is defined as the repeatability of the measurements and the accuracy indicates how close the measurements are to the actual value [19].

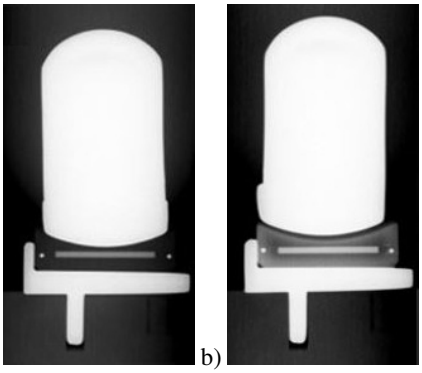

Figure 1: Standadrd radiographs taken of a) a conventional polyethylene bearing, and b) one which has been treated with Lipiodol, an oil-based contrast agent. The images demonstrate an increased visibility of the polyethylene unicompartmental knee bearings after treatment.

2. Materials and Methods

The precision and accuracy of MBRSA measurements were investigated by a series of phantom based experiments on polyethylene bearings with different radiopacity levels. The experimental methodology has been split into four sections. In the first section, the sample preparation and characterisation are explained; in the second section, the imaging set-up is explained; the third section details the experiments performed; and the fourth section specifies the data analysis performed.

2.1. Sample preparation and characterisation

Four anatomic Oxford Partial Knee (Zimmer-Biomet, Bridgend, UK) bearings (size 4) made from medical grade UHMWPE (ArCom, Zimmer-Biomet, Bridgend, UK) were used for this study. The bearings were fully finished, packaged, and sterilised with the standard 33 kGy gamma irradiation. Three of the bearings were immersed in 30 ml of the Lipiodol contrast agent, and then held at an elevated temperature of 105°C for three different durations (12 h,18 h, and 24 h) to achieve different levels of radiopacity. One bearing was left untreated as a control. After each treatment, samples were left to cool down to room temperature and then cleaned with lint free wipes. The samples were stored in their original packaging to avoid any exposure to light prior to the experiments.

The radiopacity of each bearing was calculated based on ASTM F640-12. Each bearing was radiographed alongside an aluminium calibration step-wedge, where the step thicknesses were 1, 2, 4, 6, 8, and 10 mm. The greyscale of each radiograph was measured using ImageJ software [20] and five measurements were taken

through the length of each implant. The greyscale value of the 6 step-wedge thicknesses were used to calibrate the level of radiopacity to the equivalent of aluminium thickness.

2.2. Imaging

The surface models of the bearing and the femoral components were provided by the manufacturer (Zimmer-Biomet, Bridgend, UK); all the manufacturer supplied surface models will hereafter be referred to as the original CAD models. However, the treatment to increase the radiopacity led to a dimensional change, therefore a reversed engineered (RE) specimen specific model was necessary [9]. The RE solid models of the samples were created using a laser scanner (Romer Scanner, CMS108, Hexagon Manufacturing Intelligence, Surrey, UK), which has a stated resolution of 0.30 μm. Materialise Magics software (V23, Materialise, Leuven, Belgium) was used to process the scanner data and generate the stereolithography (stl) files.

The RSA set-up consisted of two synchronised X-ray tubes (Philips MCD 105 and Philips Medio 50 CP-H, Philips, Medical Systems GmbH, Hamburg, Germany), each positioned at approximately 1500 mm above the film cassettes (350 by 430 mm) at an angle of 20° relative to the normal vector of the roentgen film, creating a 40° inclusion angle between the tubes (Figure 2). A uniplanar calibration object (Medis Medical Imaging Systems bv, Leiden, The Netherlands) made from carbon-fibre was positioned underneath or behind the phantom depending on the experiment (Figure 2). The calibration object consisted of accurately positioned tantalum marker balls (1 mm diameter) which defined the laboratory coordinate system and facilitated calibrating the RSA set-up. The x-axis of this coordinate system was directed in the medio-lateral direction (parallel to the line connecting the two foci). The y-axis was directed in the superior-inferior direction (perpendicular to the x-axis). The z-axis was directed in the postero-anterior direction (perpendicular to the image plane). Rotations along the anterior-posterior axis (Rz) described the in-plane motions and rotations along the medial-lateral axis (Rx) and superior-inferior axis described the out-of-plane rotations (Figure 2).

Two separate phantoms were used; the first determined the MBRSA systems ability to measure the position of an isolated component and consisted of a carbon fibre box with a local coordinate system defined by embedded tantalum markers. The second phantom was a representation of the lower limb, consisting of a vertical rail on a base plate with two supports upon which tibial and femoral analogues were fixed, with the ability to move the femur analogue vertically Figure 3.

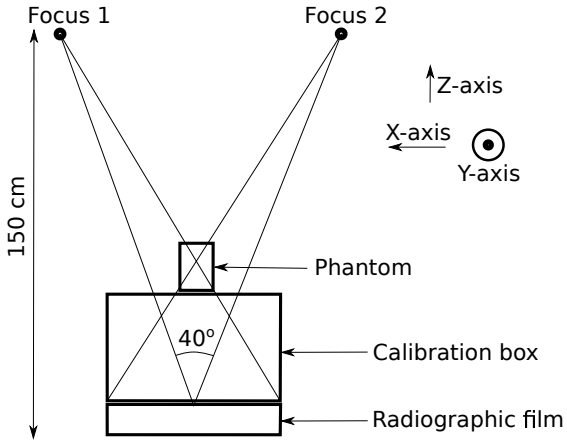

Figure 2: The RSA set-up consisting of two synchronised X-ray tubes, with a calibration box located underneath of the phantom to define the laboratory coordinate system.

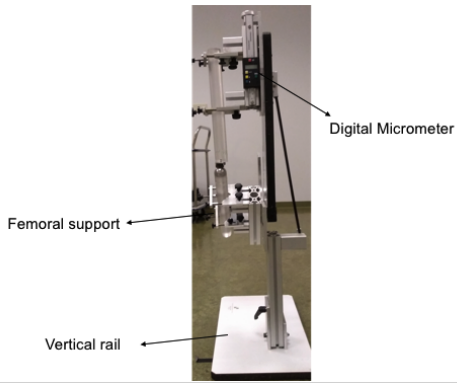

Figure 3: The setup of the standard phantom used to perform Experiments 2, 3 and 4.

2.3. Experiments

Experiment 1: RSA assessment of isolated UHMWPE components. In the first experiment, all three treated bearings and the untreated control bearing were fixed inside the carbon-fibre box phantom, with each bearing located within one of the four quadrants of the box. Twenty-six tantalum beads attached to the box phantom defined the local coordinate system, and a 30 mm thick PMMA sheet was located on the top of the box to represent the attenuation of soft tissue. The calibration object was positioned underneath the carbon-fibre box. Overall ten stereo pairs of radiographs were taken of the carbon-fibre

box together with the calibration object and all the stereo-images were analysed with both the original CAD models and RE models. The carbon-fibre box was moved as per Table 1 between measurements, to mimic clinical variation in patient positioning during an X-ray [18].

Table 1: Translational and rotational movements were applied to the phantom within the clinical range; this table specifies the direction of the movement for the carbon box phantom used for Experiment 1.

Image Number	Translation	Rotation
1	-	-
2	+X	-Y
3	+Z	-Y
4	-Z, -Y	+RZ
5	-RZ	-RZ
6	-RX	-
7	-X	-Y
8	+Y	+RZ
9	-X	+RY
10	+Z	+RX,-RY

Experiment 2: RSA assessment of UHMWPE components alongside a metal component, representing a standard metal-on-polyethylene scenario. To investigate the effect of the metal on the accuracy of the RSA measurement of the polyethylene bearing, an Oxford Partial Knee femoral component (medium size, Zimmer-Biomet, Bridgend, UK), made from cobalt-chromium alloy, was used in conjunction with the phantom representing the lower limb (Figure 3, described fully by van IJsseldijk [21]). The phantom incorporated a polycarbonate rod representing the femur, to which the metal femoral component was cemented (Biomet Bone Cement R, Zimmer-Biomet, Breda, Netherlands), and a Sawbones tibia (Sawbones USA, Washington, USA), to which the polyethylene bearing was fixed. The polycarbonate rod was mounted on a micrometer stage allowing vertical movement relative to tibia. Measurements were performed for each of the treated bearings. The phantom had 6 tantalum beads attached to the polycarbonate rod and 6 attached to the Sawbones tibia. For this set of measurements all the images were taken with the phantom arranged to simulate an upright standing position.

For each bearing seven stereo-pairs of radiographs were taken of the phantom, and between each image acquisition clinically relevant translation and rotation movements (detailed in Table 2) were applied to the phantom to replicate the variability in patient positioning during serial measurements [21]. The whole assembly was moved each time and so the true relative movement between the markers and the bearings was always zero; therefore, the calculated micromotion between the tibia and the bearing using the software represented the system precision.

Experiment 3: RSA assessment of cemented polyethylene. These experiments were performed in the same manner as for Experiment 2 but the bearings were cemented to the Sawbone and there was no metallic component. The experiments were only performed on the high radiopacity polyethylene, and the precision measured using the same procedure and movements as described for Experimernt 2.

Table 2: Translational and rotational movements were applied to the phantom within the clinical range; this table specifies the direction of the movement for the carbon box phantom used for Experiments 2 and 3.

Image Number	Translation	Rotation
1	-	-
2	+X	-Y
3	+Z	-Y
4	-Z, -Y	+RZ
5	-RZ	-RZ
6	-RX	-
7	-X	-Y

Experiment 4: Measurement of contact-loss. Contact loss conditions were simulated by moving the polycarbonate rod vertically upwards relative to the tibia using the micrometer stage, having the effect of lifting the femoral component away from the bearing. This was only performed for the 24 h treated, high radiopacity bearing. The following vertical separations were applied: 0.2, 0.5, 0.7, 1.0 and 2.0 mm. Stereo-pairs of radiographs were taken at each separation value. The phantom was re-positioned with the femoral component contacting the bearing, and each separation and measurement was repeated two more times. All the analyses were conducted with both the original CAD models and RE models.

2.4. Data analysis

All the stereo-radiographs were analysed with MBRSA software (Version 4.11, RSAcore, Leiden, Netherlands) with both the original CAD models and RE models. The stereo-radiographs were calibrated to calculate the projection parameters and then the outer contour of the components was detected in the stereo-radiographs. The digital pose estimation tool was used to minimise the difference between the detected contour and the model contour. The edge detection option in the

software was used and some manual correction was required to eliminate any unreliable detection. Calibration accuracy was assessed by performing a re-projection of the calibration points and by calculating the difference from these re-projected points to their measured positions. The accuracy of the fit between the silhouette of the CAD model of the knee replacement component and its silhouette on X-ray was determined by the ratio of the matched to the mismatched area.

For all statistical analyses IBM SPSS Statistics for Windows (Version 25, IBM Corp., Armonk, NY, USA) was used. The following statistical analyses were conducted:

- To compare mean values obtained from the different levels of radiopacity; a non-parametric Kruskal-Wallis test, with the null hypothesis that there was no difference between the results obtained from the different levels of radiopacity.
- To compare the precision of radiopaque UHMWPE with the metallic femoral component: a non-parametric Mann-Whitney U test was performed, with the null hypothesis that there was no difference between the result obtained from the radiopaque UHMWPE and the femoral component of this study and tibial trays of other published studies.
- To compare the precision in the different directions (x, y, z): a Kruskal-Wallis test was performed with the null hypothesis that there was no difference between the standard deviations of each precision obtained from each level of radiopacity.
- To quantify the reliability to which the separation distance could be measured: the intra-class correlation coefficient (ICC) was found for each level of radiopacity. Furthermore, a Bland-Altman analysis was used to evaluate any systematic bias between the RSA measurements and the physical measurement [22].

3. Results

3.1. Level of radiopacity

The level of radiopacity was converted to the attenuation through an equivalent thickness of aluminium (Figure 4). The maximum radiopacity was observed on the surface of each bearing and there was no statistical difference in the measured overall surface radiopacity (equivalent aluminium thickness) of each bearing. The radiopacity of the bearings treated for 18 and 24 hours was approximately equivalent to 3 to 4 mm thickness of aluminium. The lowest radiopacity was obtained from the central region of each sample and was approximately equivalent to 2 mm thickness of aluminium. The lowest surface radiopacity was observed in the centre of the sample treated for 12 hours. Samples treated at 18 and 24 hours showed similar greyscale values throughout the samples.

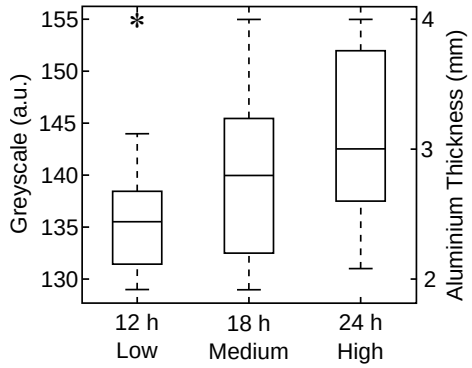

Figure 4: The greyscale values for each sample the equivalent Aluminium thickness, shown for bearings immersed in the oil-based contrast agent for 12, 18 and 24 hours to create a low, medium and high radiopacity, respectively. The equivalent thickness of Aluminium was calculated in accordance with ASTM F640-12.

3.2. Assessment of isolated polyethylene

Translation and rotations measured by the RSA software for this experiment related directly to the precision, with zero values representing perfect precision. The translational measurements in the y-direction were between -0.2 and 0.05 mm, with an average of 0.017 mm and a standard deviation (SD) of 0.06 mm (Figure 5). The standard deviation for the x-direction was moderately higher (SD: 0.127 mm), yet the overall average was at its lowest value of all the directions (mean: 0.005 mm). In z-axis, the translational precision was comparatively higher than x and y directions (mean: 0.25 mm, SD: 0.29 mm). For the rotational movements, the x- and y- precision values were closer to zero (mean: 0.12°, 0.04° and SD: 0.29°, 1.19° respectively), and the highest measurement error was observed in the z-direction (mean: 0.27° , SD: 0.46°). Overall, statistical analysis found no significant difference between the measurements in the different directions (p=0.0017 for translation and 0.003 for rotation). However, if the absolute values of precision were used instead of the signed values the precision in the y-direction would be statistically higher (p=0.02). This experiment also

showed that the the level of radiopacity did not influence the precision (p=0.09 for translation and p=0.06 for rotation).

The translational and rotational movements were also measured using the RE surface model. There was no significant difference between the measurements obtained from the RE model and the original CAD model (p=0.001), however, a lower standard deviation (0.05 for any translation) was observed when the RE surface model was used.

3.3. Metal-on-polyethylene RSA assessment

A higher precision level was observed when the PMMA sheet was removed (Figure 6) and the bearings were imaged using the lower limb standing phantom with the femoral component present. The precision of the translational movements was 0.06 mm in the x-direction, 0.03 mm in the y-direction and 0.06 mm in the z-direction, which was comparable with the metallic part (femoral component) present in this study (mean: x=0.09 mm, y=0.0316 mm, z=0.0755 mm). The statistical analysis found no difference between translational precision for the different levels of radiopacity, nor the direction of the measurements, for both the original and RE CAD models (p=0.3 and p=0.05, respectively). However, the statistical analysis showed that the precision of the measurement for rotational movements in the y-direction (y=0.224°) was statistically higher than any other direction (mean: x=0.069°, z=0.089°).

3.4. Cemented polyethylene RSA assessments

All-polyethylene prostheses are often fixed into the bone using radiopaque bone cement, so to replicate this clinical situation as closely as possible, the radiopaque UHMWPE was cemented to the tibial Sawbone and the precision measured. The lowest mean value for any translation was in the y-direction (mean: 0.008 mm, SD: 0.104 mm). The highest value measured for any rotational movement was in the y-direction (0.34°, SD: 0.37°). However, there was no statistical difference between the measurements in each direction Figure 7. It was noted that the radiopacity of the cement interfered with the detection of the lower part of the bearing and the contour selection process was less robust, but there was no significant difference between the precision values measured with or without any cement.

3.5. Contact-loss

A Bland-Altman plot was used to compare the RSA derived femoral component displacements with the applied displacement measured using the micrometer (Figure 8). Bland-Altman can be used to identify the outliers (accuracy) and the repeatability (precision) of the measurements. The horizontal lines in the plot identify the mean value and the limits of the measurements. Only one of the measurements was outside of the interquartile indicating that the RSA software was able to calculate the separation distance to within 95% of the difference of the applied value and measured by the micrometer. A clear linear correlation was also observed between the measured separation and the actual value. The Interclass correlation coefficient was calculated for each level of radiopacity (high=0.997, medium=0.998 and low=0.998).

4. Discussion

RSA analysis is recommended for post-market evaluation of hip and knee metallic implants [23]; but due to the limited attenuation of polyethylene materials model-based RSA cannot be directly used for polyethylene components. Enabling the use of model-based RSA for polyethylene parts can be beneficial for accurate quantification of positioning, diagnosing complications, *in-vivo* kinematics and wear analyses of the prosthesis.

The first part of this study confirmed that it is possible to achieve a sufficient amount of radiopacity to enable visualisation of the polyethylene component in a radiograph for RSA analysis. The level of radiopacity varied throughout the samples and since radiopacity was achieved by diffusion it was expected that radiopacity would be a function of distance from the surface and treatment duration. The highest radiopacity achieved was on the surface of the samples. The surface radiopacity of the samples treated at 18 and 24 hours were similar, suggesting that a saturation level had been achieved on the surface of polyethylene. The surface greyscale of the medium and high radiopacity bearings was on average comparable with a block of aluminium of 3 or 4 mm thickness.

The precision and accuracy of the measurements were investigated using a series of phantom based experiments. The precision for the translational movement was between 0.03 to 0.2 mm, which is comparable with results presented in the literature [18, 7] for metallic components. For the rotational movements; however, the precision was not as good as reported for metallic knee components in the literature [18]. The more precise value reported for hip/knee implants is below 0.3°, while in this study the precision value was close to 1°. A study by Holm-Glad *et al.* [7] on wrist implants reported rotational precision of up to 2° which is similar to the results of this study [7]. It is possible that the small

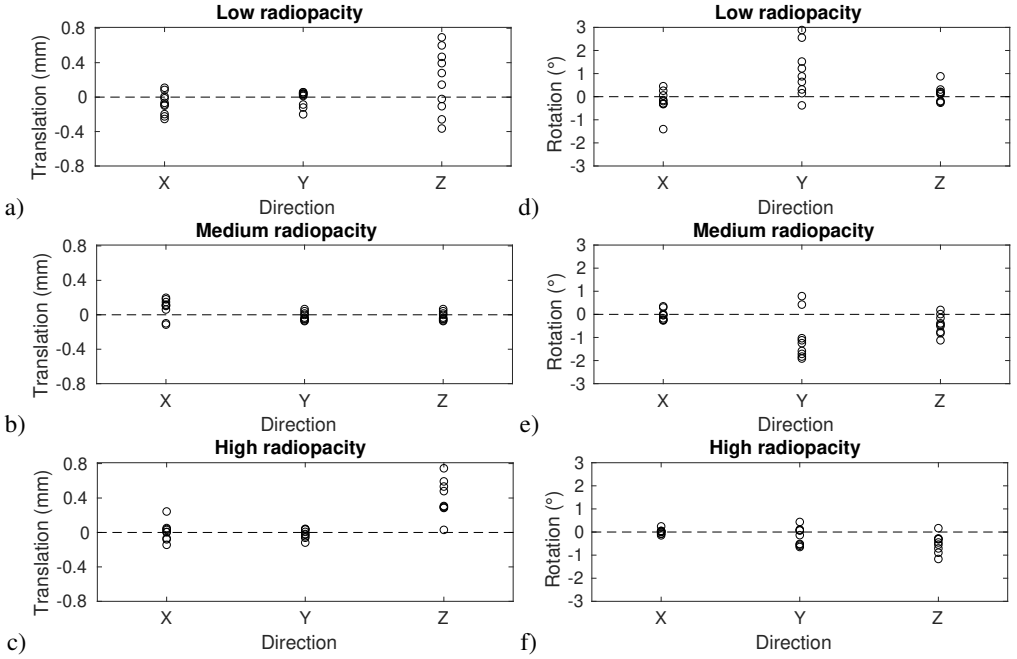

Figure 5: Translational and rotational measurement error calculated for the isolated polyethylene components (Experiment 1). Results shown for low radiopacity knee bearings (a, d), medium radiopacity bearings (b,e) and high radiopacity bearings (c,f), measured by the RSA software using the original CAD model.

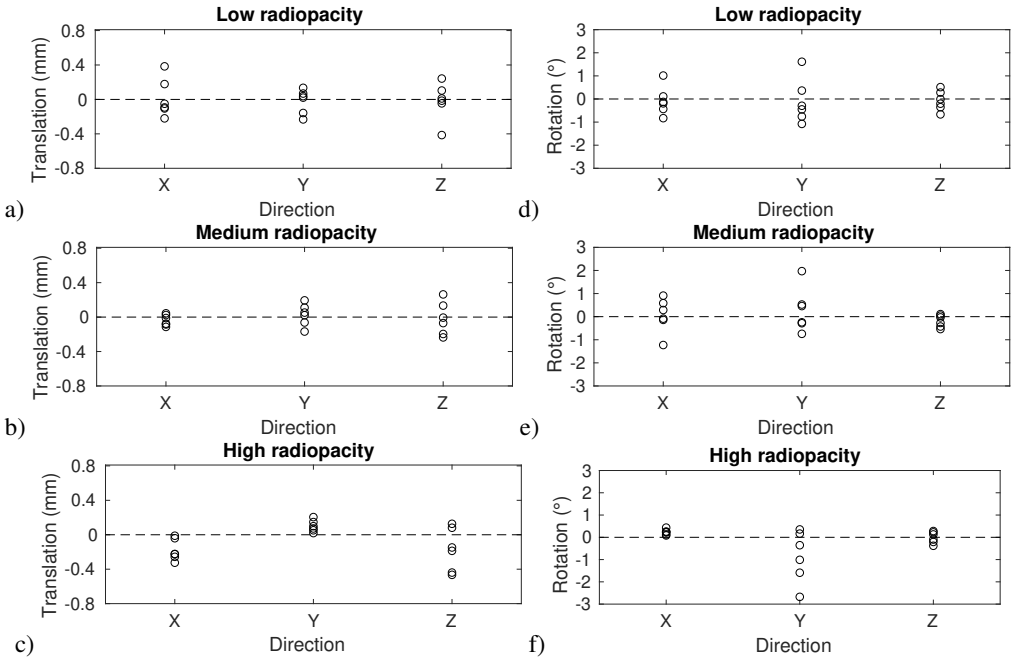

Figure 6: Translational and rotational measurement precision calculated for the polyethylene knee bearings within the standing phantom alongside the metallic components (Experiment 2). Results shown for low radiopacity knee bearings (a, d), medium radiopacity bearings (b,e) and high radiopacity bearings (c,f), measured by the RSA software using the original CAD model.

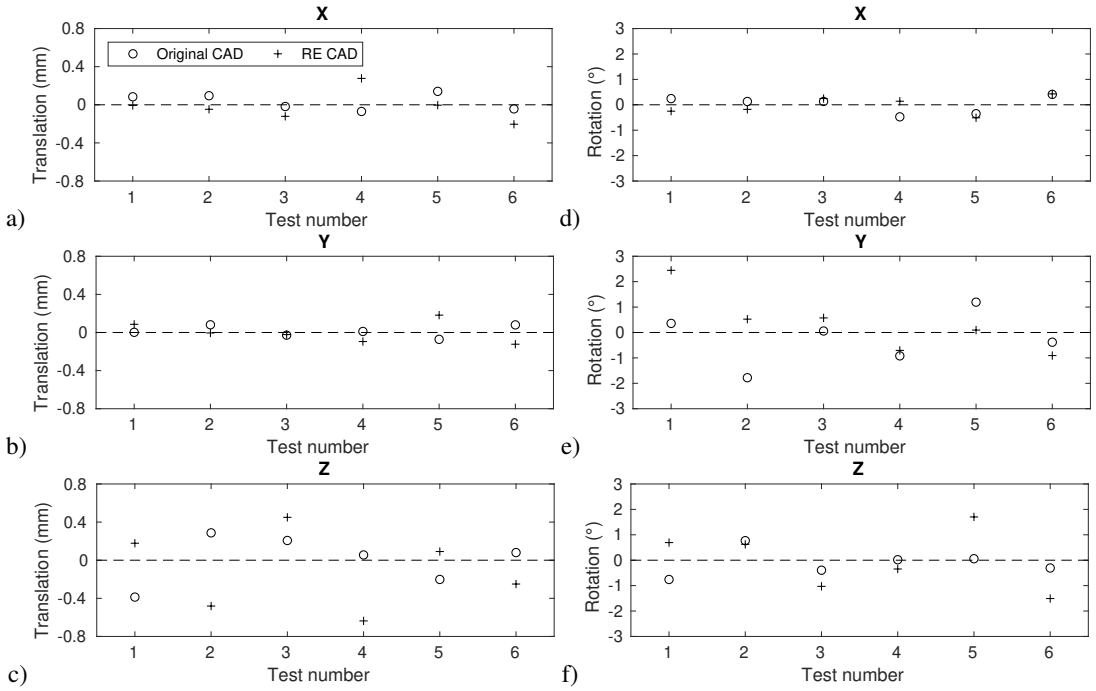

Figure 7: Translational and rotational measurement precision calculated for the polyethylene knee bearings within the standing phantom when cemented directly to the tibial Sawbone (Experiment 3). Results shown only for the high radiopacity bearing. Results shown when measured by the RSA software using the original CAD model, and the reverse engineered (RE) CAD model.

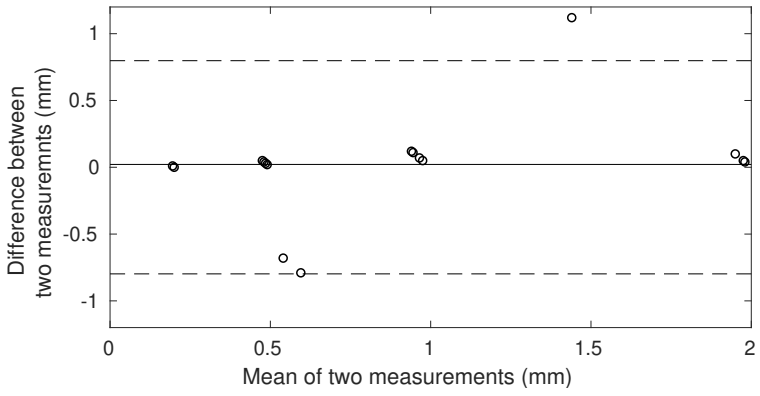

Figure 8: Bland-Altman plot of the difference between the known separation distance (Experiment 4), and the distance between the components measured using the RSA software. Measurements shown using the original CAD model.

size and high symmetry of the prosthesis reduced the precision level [24]. Both partial knee and the wrist implant components are smaller and more symmetric than total knee components. In order to minimise the effect of the symmetry on the RSA measurements, the inner contour of samples was used rather than the outer surface for RSA analysis. In metallic implants, due to the higher level of radiopacity the outer contour provides a sufficient number of points to accurately match the 3D surface model with the virtual projection of the implant.

Another factor, other than size and shape of the implants, affecting the model-based RSA is the accuracy of the surface model [17]. The measurements only can be as accurate as accuracy of the surface model. Due to machining and manufacturing tolerances, the CAD model provided by the manufacturer may not a perfectly accurate representation of the sample geometry. Furthermore, the Lipiodol treatment used to introduce the radiopacity also causes a significant dimensional change (up to 28% increase) in the samples [13]. A RE model was created to better represent the actual component; but unfortunately we were unable to achieve a high accuracy with the RE model. This may have been becase the laser scanner used to create the RE model had an accuracy lower than ones used in other studies (0.30 microns compared to 0.13 microns reported in other studies [17]); but also UHMWPE is a transparent material which can reduce the quality of the reversed engineered scans.

Another possible factor affecting the precision of the result is the radiopacity level of the samples, The highest level of radiopacity achieved was equivalent to a 4 mm block of aluminium, which was sufficient for visualisation of the samples; however, the low and uneven distribution of the radiopacity caused complications and mismatch during the contour detection. It was necessary to manually remove these unreliable contours and at times this resulted in the exclusion of a large portion of the contour. For metallic implants previous studies have shown that in a tibial implant the accuracy was not affected by excluding 50% of the contour [24], although reduction in the contour may increase the variability in the measurement. A higher level of radiopacity may be achieved if the diffusion process occurs prior to cross-linking [25]. Due to manufacturer limitations, in this study the diffusion process was performed after the crosslinking process which may have hindered the diffusion of the Lipiodol and reduced the radiopacity [26].

A potential application of radiopaque polyethylene is to enable the quantification of wear directly, which is often longitudinal [27] and occurs in the z-direction. Currently wear measurements are inferred from the position of the metallic components; however, contact-loss or microseparation of bearings away from the femoral component has been reported in many studies which can introduce error [7]. Dynamic RSA has been used to measure contact-loss by monitoring the distance between the femoral and tibial component during exercise; contact-loss of between 0.3 and 1.5 mm was measured during cycling and 0.24 to 0.35 mm during step motion [7]. The results of the contact-loss measurements performed in the present study suggest that it is possible to calculate the separation directly from the polyethylene with sub-millimeter accuracy in the z-direction. The Bland-Altman graph (Figure 8) confirmed a strong agreement between the manually measured and RSA measured distances.

We acknowledge the limitations of this study, one of which is the lack of *in vivo* data. Radiopaque UHMWPE is a novel material and it has not been used clinically yet. Thus, our conclusion is limited to the results obtained from the phantom experiments. The precision of phantom studies is typically two to three times lower than the clinical data [17]. Even though it is not possible to fully replicate all the clinical variables, this study attempted to reproduce the clinical situation as closely as possible. A 30 cm of PMMA sheet was used to replicate the soft tissue attenuation, this amount of PMMA agrees with value calculate from the algorithm used in the Delft university for a hip study (unpublished internal report [28]); currently, there is no study to validate PMMA thickness for a knee model. Also, a 50 mm diameter polycarbonate rod was used to replicate the bone X-ray attenuation of the femur. This study was also limited in that the experiments were conducted for a single size implant with a small number of samples. For future studies, the experiments will be repeated for total knee bearings which have a lower symmetry and to investigate the impact of improving the quality of the laser scanning so that the CAD model more closely matches the geometry of the polyethylene part.

5. Conclusion

This paper introduced a novel type of polyethylene which has an X-ray attenuation high enough to be visualised in radiographs. The results demonstrated that radiopaque polyethylene bearings can be analysed with model-based RSA with a precision less than 0.06 mm for translational movements and more than 95% accuracy. However, factors such as the limited level of radiopacity, component symmetry and the accuracy of

the surface models limited the precision of the measurements. More work is required to refine the procedure and better understand its limitations, but this study demonstrates the promise of the technique and is the first to perform RSA directly on a polyethylene component.

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4.2 Summary

The research in this chapter demonstrated the potential for radiopaque polyethylene for use in medical imaging applications. In Chapter 3 the optimal treatment conditions were selected for the Lipiodol diffusion into polyethylene which maximised the radiopacity while maintaining the mechanical properties. In the present chapter the optimised treatment has been applied to knee bearings, and those bearings could be clearly seen in X-ray radiographs and used successfully for MBRSA measurements. This is the first time that MBRSA has been used to take measurements directly of a polyethylene implant, and it has great potential for post-market surveillance. The key findings of this chapter are summarised below.

- It was possible to identify the projection of the radiopaque bearings on standard X-rays and stereo-radiographs, confirming the functionality of the radiopaque polyethylene and its feasibility for MBRSA applications.
- The diffusion treatment caused the samples to swell, leading to a slight difference between the original computer-aided design (CAD) geometry and the sample. Consequently a reverse engineered CAD model was created, but the optical properties of the material and the resolution of the scanner introduced further error. Thus for MBRSA to be used reliably with the radiopaque polyethylene, the protocol would need to include a high resolution laser-scanning step for optimal precision.
- The precision of the measurement for translational movements was equivalent to that of MBRSA performed on metallic implants. MBRSA is considered to be gold standard method for post-market surveillance due to its high precision which means only a small number of patients is required for a thorough clinical investigation. The results confirm that all-polyethylene should be made of radiopaque polyethylene to be able to do a thorough clinical investigation in a short time.
- The precision of the measurement for rotational movements was lower than observed for metallic implants, and this may have been due to the high symmetry of the implants. It is likely that a higher rotational precision could be achieved using a total knee bearing and a better quality surface CAD model. Although the precision of rotational movements was lower than reported results for femoral component, it was comparable to the results of studies for smaller implants such as for elbow replacement.
- The accuracy of the measurement was more than 95% in superior-inferior direction. This shows the potential for radiopaque polyethylene to be used for wear analysis because polyethylene wear in joint replacements generally occurs in the superior-inferior direction. As explained in the literature review, wear is a common complication and achieving an accurate clinical measurement of wear can be challenging.

Chapter 5

A practical model of the diffusion of oil–based fluid into polyethylene

5.1 Context

As explained in the literature review provided in Chapter 2, oily fluids such as vitamin E can be can be incorporated into polyethylene using two different methods. In the first method vitamin E is added to polyethylene resin prior to consolidation and in the second method vitamin E is diffused into the consolidated part [1]. All but one (Zimmer-Biomet) of the current orthopaedic manufacturers use the first method for their vitamin E polyethylene implants, even though the presence of vitamin E in the polyethylene during the irradiation reduces the efficiency of the cross-linking. This may well be due to the manufacturing challenges involved in achieving an even distribution of vitamin E in the part and the lengthy processing steps [45].

An elevated temperature is required to incorporate vitamin E into polyethylene using diffusion; the temperature should not be so high that it causes a reduction in crystallinity, but also must be high enough to achieve an adequate amount of antioxidant. The infusion of vitamin E often results in a significant dimensional change (10 to 15%) and swelling of the surface. The swelling is associated with the accumulation of vitamin E under the surface, and so manufacturers include a subsequent homogenisation step to achieve an even distribution of vitamin E throughout the part [45]. Different implant geometries, sizes, and features present individual challenges for achieving the desirable homogenisation of the additive throughout the material, and so the manufacturing processes for each implant need to be identified using trial and error, which is insufficient, expensive and unpredictable.

Attempts have been made to analytically model the diffusion of vitamin E into polyethylene to better inform manufacturing processes. Oral *et al.* created a 1-dimensional Fickian model of the behaviour[46] and concluded that the fit of the overall model was good, but on inspection it is clear that the fit of the model was spatially dependent and had significantly more error in the centre of the sample. There is scope to create a more representative model of the diffusion of oil within polyethylene. It is likely that the mechanism of the diffusion will be similar for vitamin E infused polyethylene as it is for Lipiodol infused polyethylene, and so a Fickian-based diffusion can be assumed.

The goal behind the distribution of oil within the polyethylene is slightly different for Lipiodol compared with vitamin E. For vitamin E polyethylene an even distribution of the anti-oxidant throughout the part is desirable so that no oxidation occurs within the part. Whereas for radiopaque polyethylene there could be regional variation with a higher concentration of Lipiodol at the surface, provided it is sufficient to visualise on an X-ray. Furthermore, for cost-efficiency it is sensible to use the minimum volume of Lipiodol, and so creating a part with a radiopaque outline would use less Lipiodol than achieving a similar radiopacity throughout the whole part. For these reasons a homogenisation step would not be necessary for the radiopaque polyethylene.

The paper presented in this chapter uses numerical modelling approaches to develop a simple FE-based Fickian model and compares the accuracy of 1-, 2-, and 3-dimensional models. The application of the developed model is not limited to Lipiodol, or the medical industry, as the model has the capability to be used for diffusion of any oil-based fluid into polyethylene materials.

Appendix 6B: Statement of Authorship

This declaration concerns the article entitled:			
Practical model of the diffusion of oil-based fluid into polyethylene.			
Publication status (tick one) **Draft manuscript** [x] **Submitted** [ ] **In review** [ ] **Accepted** [ ] **Published** [x]			
Publication details (reference)	Fedra P, Zaribaf. , Tahir, Hassuji., Andrew N, Cookson,. Harinderjit S. Gill,(2020). DOI: 10.1002/app.50028		
Copyright status (tick the appropriate statement) I hold the copyright for this material [ ] Copyright is retained by the publisher, but I have been given permission to replicate the material here [x]			
Candidate's contribution to the paper (provide details, and also indicate as a percentage)	The candidate considerably contributed to the The candidate contributed to the "**Formulation of ideas**", alongside Dr Elise Pegg and Prof Gill The candidate considerably contributed to the "**Design of methodology**": Dr Cookson teaches a course on modelling of diffusion and methodology presented in the course has been tailored for this application by the candidate and Dr Elise Pegg The candidate conducted the "**experimental work**" and Tahir had a very significant contribution in the development of the model. Dr Elise Pegg supervised the work. The candidate considerably contributed to the "**presentation of data in journal format**": The candidate drafted the original manuscripts which has been revised by all the co-authors. Both Dr Elise Pegg significantly contributed to improve the quality of the manuscript and assisted with data visualisation.		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
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A practical model of the diffusion of oil-based fluid into polyethylene

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Abstract

It is possible to modify the properties of semicrystalline polymers using diffusion to introduce additional functionality. For example, Vitamin E infused polyethylene has antioxidant properties, which enhances the longevity of the polyethylene. Lipiodol ultra fluid, an iodinated oil-based contrast agent, can be used to enhance the X-ray attenuation of medical grade polyethylene. To manufacture a part geometry with a sufficiently even distribution of oil for radiopacity, while maintaining the thermally dependent properties of the polymer (e.g., crystallinity) is a challenge. Rather than relying on trial and error, this study aimed to identify the simplest, most practical model, which could assist with planning for manufacturing of such parts. Models in 1D, 2D, and 3D were examined but only the 3D Fickian model was able to predict the profile of oil diffusion within polyethylene with suitable performance (as low as 7% inaccuracy for some diffusion conditions). The model was more accurate at the surface of the samples and at lower diffusion temperatures. The 3D Fickian model used in this study was capable of estimating the oil concentration in the surface of a polyethylene part after diffusion to a sufficient accuracy for planning manufacturing processes of oil-infused polyethylene parts.

KEYWORDS

adsorption, biomedical applications, manufacturing, polyolefins, theory and modeling

1 | INTRODUCTION

Polyethylene is one of the most commonly used materials in medical applications due to its acceptable biocompatibility;[1] high-density polyethylene foam is used for maxillofacial implants,[2] and ultrahigh molecular weight polyethylene (UHMWPE) is commonly used for bearing surfaces in orthopedic applications or for ligament replacements or sutures.[3]

The lipophilicity of oily fluids makes them partially soluble in polyethylene enabling diffusion[4] and they can be used to alter the mechanical, physical, and chemical properties of polyethylene. Oil-based dyes can change the color of polyethylene packaging materials.[5] Oil-based antistatic agents (e.g., ethoxylated fatty acid amines) can reduce dust attraction or improve the handling behavior of thin polyethylene films.[5] Antioxidants such as Vitamin E (α-tocopherol) which is a natural oil-based antioxidant can be used to enhance the oxidative stability of polyethylene, and has been used for packaging and medical applications.[6] Another oil-based fluid suitable for medical applications is Lipiodol which is an iodised oil contrast

agent containing naturally occurring fatty acids (e.g., α tocopherol, linoleic acid)[7] that can enhance the radiopacity of polyethylene to facilitate post-operative follow-up of medical devices.[8] For medical applications oil, once contained within polyethylene, has the advantage of being less soluble in aqueous body fluids, which reduces the rate of leaching,[9] but it is nevertheless essential that the oil does not cause any adverse biological reactions.

There are two possible ways to incorporate oil into polyethylene. The first method is to mix the oily fluid (e.g., Lipiodol) with the polyethylene resin prior to consolidation, resulting in an even distribution of oil through the part, and perform cross-linking and machining if required in the same manner as for a standard polyethylene part. However, the antioxidant properties of some oils (Vitamin E or Lipiodol) can deactivate the free radicals required for cross-linking and so reduce the efficiency of cross-linking.[10] Cross-linking increases the tensile strength and wear resistance of the polyethylene, and is essential for high-performance applications such as for joint replacement bearings.[11] The second method is to mold and machine the part into the final geometry, cross-link the part, and then diffuse the oil into the polyethylene as the last stage so that the cross-linking is unaffected. However, this presents many challenges. For instance, the part geometry may have small features, which can become saturated with oil more quickly than the bulk, making it difficult to attain an even distribution of oil. To accelerate the diffusion process an elevated temperature is required and the increased temperature can change the material properties of the polyethylene; such as its tensile strength and chemical stability, but it will also influence factors relating to the diffusion such as the saturation concentration. The temperature can also change the geometry of the part due to the release of residual stresses from the previous processing steps and due to the swelling of the surface with the diffusant.[9] Most importantly, temperature above the melting point of polyethylene can alter the crystallinity content of polyethylene and therefore the treatment temperature should be kept below the melting point to avoid any alteration in the critical properties of polyethylene. Polyethylene has a melting point around 413 K and it is necessary to carefully determine the temperature at which diffusion of oil into polyethylene is performed. The challenges in balancing the diffusion parameters and achieving the required product performance mean very few manufacturers perform the diffusion as a last step, despite its potential benefits.

Unfortunately, information on the diffusion of oil-based fluids into medical polyethylene, or semicrystalline polymers in general, is limited, and the uptake and leaching of molecules from and into polyethylene cannot be easily predicted. Semicrystalline polymers (e.g., polyethylene) consist of crystalline regions embedded in amorphous matrices. Macromolecules are only able to travel through the amorphous regions, with the crystalline regions hindering the diffusion pathway of the macromolecules;[9] this is even true for small gas molecules.[12] This introduces many unknown factors related to the diffusion process and structural changes of the semicrystalline polymers with temperature, which can be difficult to investigate experimentally. To manufacture a part with an even distribution of oil, while maintaining these complex thermally dependent properties of the polymer is a challenge. Using computational models to optimize and plan diffusion treatments such as this can vastly reduce development costs.

The three key models, which have been created to predict the diffusion of small molecules into semicrystalline polymers are summarized in Table 1.[6,13,14] Fick's law of diffusion has been used as the starting point for the majority of these models. A more specific model for polyethylene was developed by Oral et al. which predicted the diffusion of small lipophilic molecules, such as Vitamin E, into the surface of polyethylene[6]; however, the study did not quantify the model accuracy as a function of depth, and based on the plots of Vitamin E concentration at different depths presented in the study it can be seen that the fit of the model was poor in the central regions of the samples. One of the main limitations of Oral's model was that it was developed in only one dimension (1D) which may be too simplistic. A more general model was developed by Crank, which suggested a history-dependent diffusion coefficient for semicrystalline polymers that varied with concentration and time.[13] Crank's model assumed that there was a sharp boundary between an inner core and the outer region of the polymer and that this boundary was able to move with

TABLE 1 Summary of the Fickian-based models developed to predict the diffusion of small molecules in semicrystalline polymers

Author	Model of	Assumptions
Oral[6]	Polyethylene and lipids	Saturation concentration reached instantly
Crank[13]	History-dependent diffusion	Discontinuous diffusion coefficient Saturation concentration reached instantly
Long and Richman[14]	Time-dependent surface concentration	Constant diffusion coefficient

TABLE 2 Geometry and treatment of the polyethylene samples used for the diffusion experiments

Sample type	Dimensions	Cross-linked	Time (h)	Temperature (K)
Cuboid	15 x 10 x4 mm	No	12, 24	358, 378, 398
dogbone	IS0-527b annex AB	No	12, 24	358, 378, 398
Knee bearings	Oxford partial knee, Size 4	Yes	24	378

time causing an alteration in the diffusion coefficient (discontinuous diffusion coefficient). Both Oral's and Crank's Fickian models assumed that the surface concentration instantaneously reached its maximum value (saturation concentration). On the other hand, Long and Richman developed a model, which assumed a time-dependent surface concentration[14] where there was a constant diffusion coefficient but the surface concentration changed. The surface concentration was divided into two stages; an instantaneous surface concentration followed by a slow drift toward an equilibrium value, based on the molecular relaxation process in semicrystalline polymers.[14]

This study tests the limits of Fickian-based diffusion models and examines whether it is possible for a Fickian-based model to predict the diffusion of oily fluids (Lipiodol) into polyethylene parts. For practical implementation the simplest Fickian model which could fit the data was preferred, and so 1D, 2D, and 3D models were developed. Each model was fitted empirically to the experimental data and then the most suitable model was validated against experimental data from new geometries and the accuracy assessed.

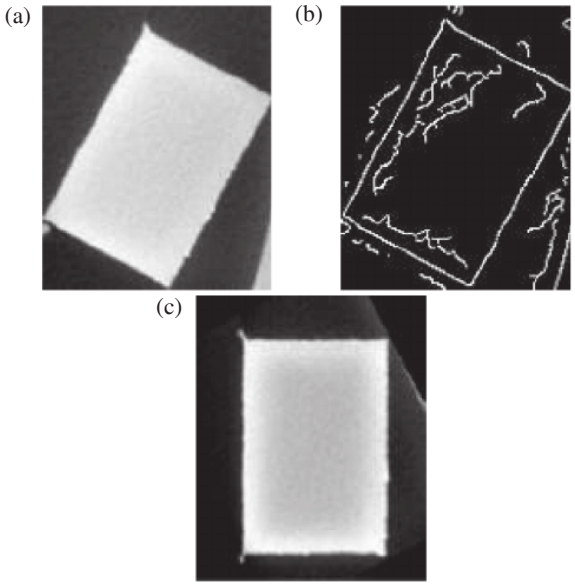

FIGURE 1 (a) DICOM image of UHMWPE cuboid sample prior to alignment, (b) DICOM image of UHMWPE cuboid after Canny edge detection, (c) DICOM image of UHMWPE cuboid sample post alignment. DICOM, digital imaging and communication in medicine; UHMWPE, ultrahigh molecular weight polyethylene

2 | MATERIALS AND METHODS

The experimental method has been divided into five main sections. First, the radiopaque diffusion treatment of the polyethylene samples is described. Second, the image processing methods used to determine the Lipiodol concentration profiles through the samples and to identify the parameters of the model are detailed. Third, the application of the experimental parameters to the 1D, 2D, and 3D models are outlined. Fourth, the optimization algorithm used to identify the best fit between the model and the cuboid test sample data is explained. In the fifth and final part, the validation of the most suitable model when applied to samples with different geometries is detailed, along with the method used to quantify the model accuracy.

2.1 | Sample preparation

Three different types of samples were used for this study (Table 2). Lipiodol ultra fluid (Guerbet, France) was diffused into polyethylene samples under a range of elevated temperatures (358, 378, 398 K) for either 12 or 24 h. All the cuboid and dogbone-shaped samples were made from unirradiated medical grade UHMWPE manufactured from GUR 1050 molded UHMWPE sheets from Celanese (Oberhausen, Germany). The knee bearings (anatomic Oxford Partial Knee mobile bearings size 4) were made from medical grade UHMWPE (ArCom), and were fully finished, packaged, cross-linked, and sterilized with the standard 33 kGy gamma irradiation (Zimmer-Biomet, Bridgend, UK).

2.2 | Image processing

Each sample was imaged using a μCT scanner (X Tec, XT H 225 ST, Nikon Metrology UK Ltd, Derby, UK) and the

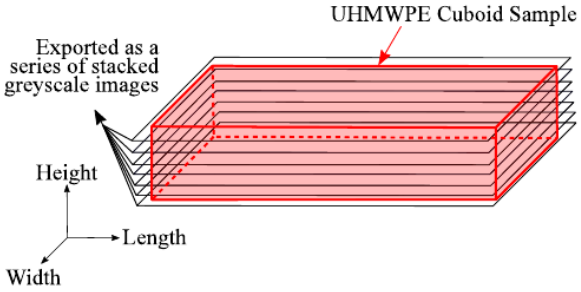

FIGURE 2 Visual representation of a DICOM image export for the UHMWPE cuboid sample. DICOM, digital imaging and communication in medicine; UHMWPE, ultrahigh molecular weight polyethylene [Color figure can be viewed at wileyonlinelibrary.com]

scanning protocols were the same for all samples (162 kV, resolution 0.2 mm) (Figure 1). Water in a plastic vial was included in the scanning chamber for calibration purposes, the Hounsfield units (HU) were scaled using water and air. The scientific data visualization software Avizo (Version 9.2.0, Thermo Fisher Scientific, Waltham, MA) was used to convert CT files (voxel file format) to DICOM (Digital Imaging and Communication in Medicine) image slices (Figure 2). A MATLAB (R2017B, The MathWorks Inc., Nattick MA) script was used to process the DICOM files. The MATLAB script isolated the region of each sample by detecting the edges using the Canny algorithm (Figure 1). The Hough transform function was used to identify the angle of rotation and applied a rotation to align the part with the horizontal. Last, the script cropped the image horizontally and vertically to just include the sample region by identifying the edges of the component (Figure 1). After processing, the greyscale values were converted to Hounsfield units. The radiopacity has been shown in previous studies to positively correlate linearly with the concentration of Lipiodol within polyethylene,[7] and so hereafter HU will be used to represent concentration in the calculations.

For the 1D model, data were compared to linear HU profiles taken through the center of the cuboid samples along both the length (15 mm profile), and the width (10 mm profile). These were taken using the improfile function in MATLAB. For the 2D model, the DICOM slice corresponding to the central plane through the thickness was used (at 2 mm height). For the 3D model, the whole volume was used to compare with the model.

2.3 | Modeling diffusion

Diffusion was modeled according to Fick's second law, which in three dimensions can be written as Equation (1):

$$\frac{\partial c}{\partial t} = D\nabla^2 c\,,\ \text{where}: \nabla = \left(\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}\right), \tag{1}$$

where c is the concentration of oil, t is time, and D is a spatially constant, scalar diffusion coefficient. 1D, 2D, and 3D versions of this model were solved using the finite element (FE) method, to determine which models were capable of accurately representing the experimental data. For the 1D case a simple in-house code was written, whereas for 2D and 3D the MATLAB PDE Toolbox was used.

2.4 | 1D model

The initial model simplified the problem to one dimension, either through the sample length or width with the corresponding 1D form of (Equation (1)) used. A simple 1D FE solver was written in MATLAB that discretised the domain into equisized elements, with linear nodal Lagrange basis functions used. A Galerkin formulation was applied to the weak form (or weighted residual form) of the diffusion equation, which was discretised in time using the Crank–Nicolson scheme due to its unconditional numerical stability for diffusion problems. Numerical integration was performed using Gauss-Legendre quadrature.

The time integration scheme was initialized from the input diffusion domain, the initial condition, time, surface concentrations, and diffusion coefficient. The surface concentration (C_s) and initial condition (C_0) were quantified directly from the surface radiopacity of the treated and untreated control samples, respectively, in the μCT data. The diffusion coefficients were calculated from the one-dimensional form of Fick's second law (Equation (1)), for just the surface region, up to a depth of 2 mm. The concentration at each distance (x) and time (t) was used, (C_x), to perform the linear regression where the gradient in Equation (2) is equal to $\frac{1}{2\sqrt{Dt}}$.

$$\frac{C_x - C_0}{C_s - C_0} = 1 - erf\left(\frac{x}{2\sqrt{Dt}}\right),\ \text{where } erf \text{ is the error function.} \tag{2}$$

The experimentally identified diffusion coefficient was used as the starting point, but this was changed during the optimisation of the 3D models (detailed in Section). The Dirichlet boundary conditions were applied at each end of the domain. To ensure accuracy in the results, the Courant–Friedrichs–Lewy condition in Equation (3) was used to set up a time step Δt appropriate for the mesh element size Δx.

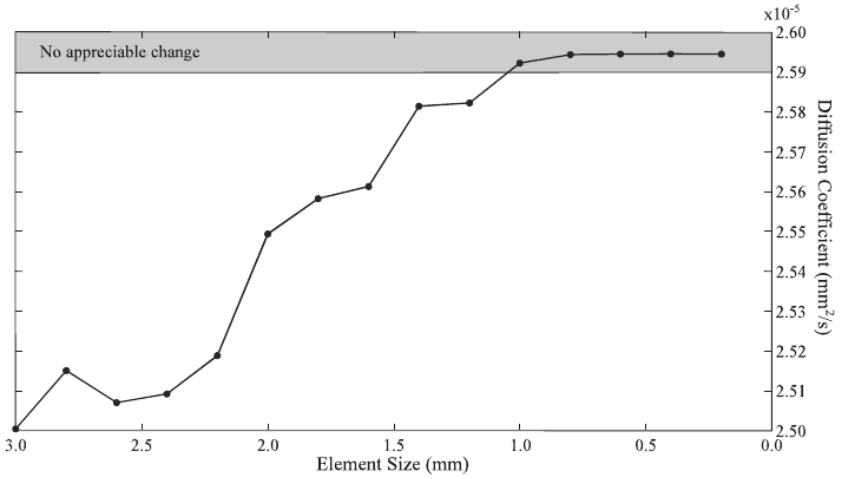

FIGURE 3 Mesh convergence study for cuboid UHMWPE sample. UHMWPE, ultrahigh molecular weight polyethylene

$$\frac{D\Delta t}{\Delta x^2} \leq \frac{1}{2}. \quad (3)$$

2.5 | 2D and 3D models

To simplify the coding complexity, the 2D and 3D Fickian-diffusion models were created and solved through the FE method via the MATLAB PDE toolbox, but aside from the dimension the parameters for the analysis were the same. For the 2D and 3D models second-order quadratic elements were applied (triangular and tetrahedral, respectively). A mesh convergence study was conducted in which the maximum element size was varied and the output diffusion coefficient measured (Figure 3). The diffusion coefficient converged to within an acceptable error (0.1×10^{-6} mm^2/s, ~0.5% error) at an element size of 1.0 mm for the cuboid component.

2.6 | Diffusion model fitting

In this stage the experimental data and 3D FE model came together to determine a value for the diffusion coefficient which result in the optimum model fit at a given time and temperature. The optimization was conducted on the experimental data from the cuboid samples and the algorithm used was a single variable nonlinear minimisation solver with bounds using a trisection method (fnminbd, Optimisation toolbox, MATLAB2017b), with the optimisation target of identifying the diffusion coefficient which resulted in the minimum root mean square error (RMSE) (Equation (4)) between the experimental data and the model. The algorithm allowed the diffusion coefficient to be changed freely. To further enhance the fit between the model and the experimental data, RMSE optimization was repeated with an additional parameter (surface concentration), which was changed within boundaries to accommodate for experimental errors (±40 HU). Each μCT scan voxel in the diffusion domain was compared with its closest matching nodal point from the diffusion model data. A tolerance was set such that the diffusion coefficient would be calculated to a precision of $\pm 0.1 \times 10^{-6}$mm^2/s which matched the accuracy of mesh convergence study. To ensure the result was converging on the global minima, a series of different starting points and upper/lower bounds were tested.

$$\mathrm{RMSE} = \sqrt{\frac{\sum_1^n (\text{Model-Experiment})^2}{n}}, \quad (4)$$

where n is the total number of voxels.

2.7 | Validation of the diffusion model

To assess and quantify confidence in the predictive capability of the fitted 3D model, it was validated against the experimental data from different geometries (Oxford Partial Knee mobile bearings and dogbone tensile test samples). The fitted diffusion coefficients and boundary conditions were applied to the new geometries. The validation was performed by comparing the difference between the experimental data and the model output for each voxel; these were assessed on a spatial basis as well as for the overall volume.

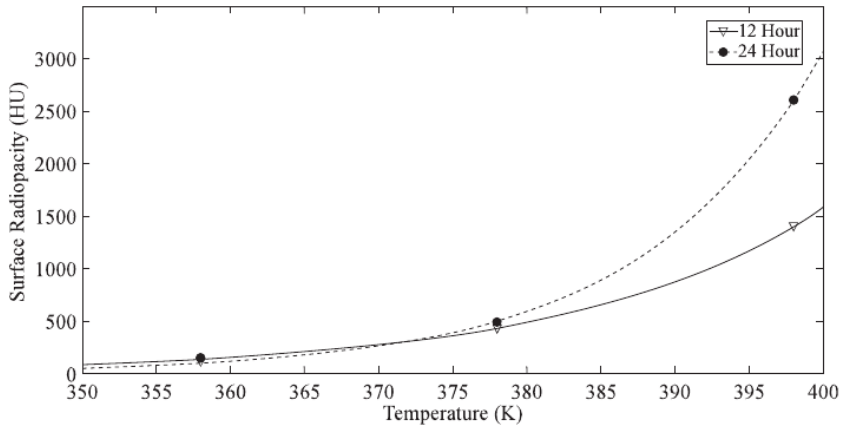

FIGURE 4 Surface radiopacity of polyethylene cuboids immersed in Lipiodol at different temperatures for 12 and 24 h, where the solid line shows the results for samples immersed in Lipiodol for 24 h and the dotted line represents the samples immersed for 12 h

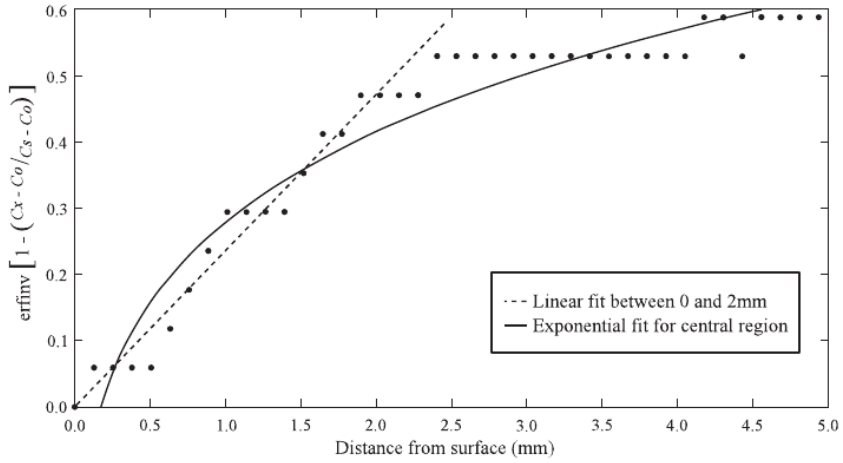

FIGURE 5 Relationship between the inverse Gaussian error function and distance, where at the outer surface (between 0 and 2 mm) a linear relationship was observed, and the central and inner regions showed an exponential relationship

TABLE 3 The diffusion coefficients (mm^2/s) for each treatment condition found by fitting the experimental data to the 1D form of Fick's second law of diffusion

	12 h	24 h
358 K	2.2×10^{-5}	7.5×10^{-5}
378 K	1.6×10^{-4}	6.4×10^{-6}
398 K	2.7×10^{-5}	3.3×10^{-5}

3 | RESULTS

3.1 | Experimentally determined diffusion parameters

The radiopacity at the surface of the samples increased with treatment temperature and time, and the relationship appeared a Fickian-type diffusion (Figure 4). However, the linear regression expected from Fickian theory according to Equation (2) was valid only up to 2 mm of the surface and with increasing the distance toward the inner region of the component; an inverse exponential relationship was observed (Figure 5). The diffusion coefficients had a high sensitivity to relatively small changes in gradient, and experimental scatter introduced large error in the diffusion coefficients (Table 3).

3.2 | 1D model

All the 1D models fit the concentration profile for the polyethylene samples closely at the surface, but in the center of the component the model was not able to match the experimental data which formed a plateau. For example, the model of radiopaque polyethylene diffused at 378 K for 24 h had the input parameters summarized in Table 4 for the 10 mm profile across the sample width. The concentration profile between the model and experimental data (Figure 6(a)) followed a similar gradient near the surface of the cuboid (<2 mm, >8 mm), but in the

central region of the component the experimental profile was significantly flatter than what the model suggests. The same trend was seen when modeling the profile along the sample length (Figure 6(b)) but it was more pronounced due to the increased length of the profile. The 1D model, which was the closest fit to the data was the 358 K condition at 24 h (Figure 7), where the initial condition resulted in a lower limit that caused a similar plateau to that observed in the experimental data.

TABLE 4 Experimentally derived input parameters used in the 1D diffusion model at 378 K for 24 h

Parameter	Input
Domain	x = 0 mm to x = 10 mm
Initial condition	−200 HU
Time	24 h
Boundary condition values	Radiopacity (0 mm, t) = 553 HU (Dirichlet) Radiopacity (10 mm, t) = 553 HU (Dirichlet)
Diffusion coefficient	6.4 × 10–6 mm2/s

Abbreviation: HU, Hounsfield units.

3.3 | 2D model

The Fickian 2D model fit was similar to that observed in 1D, where the model matched well at the surface (95% agreement with experimental data) but failed to predict the radiopacity in the central regions (Figure 8).

3.4 | 3D model

The three-dimensional Fickian-diffusion model matched the shape of the experimental data more closely than the

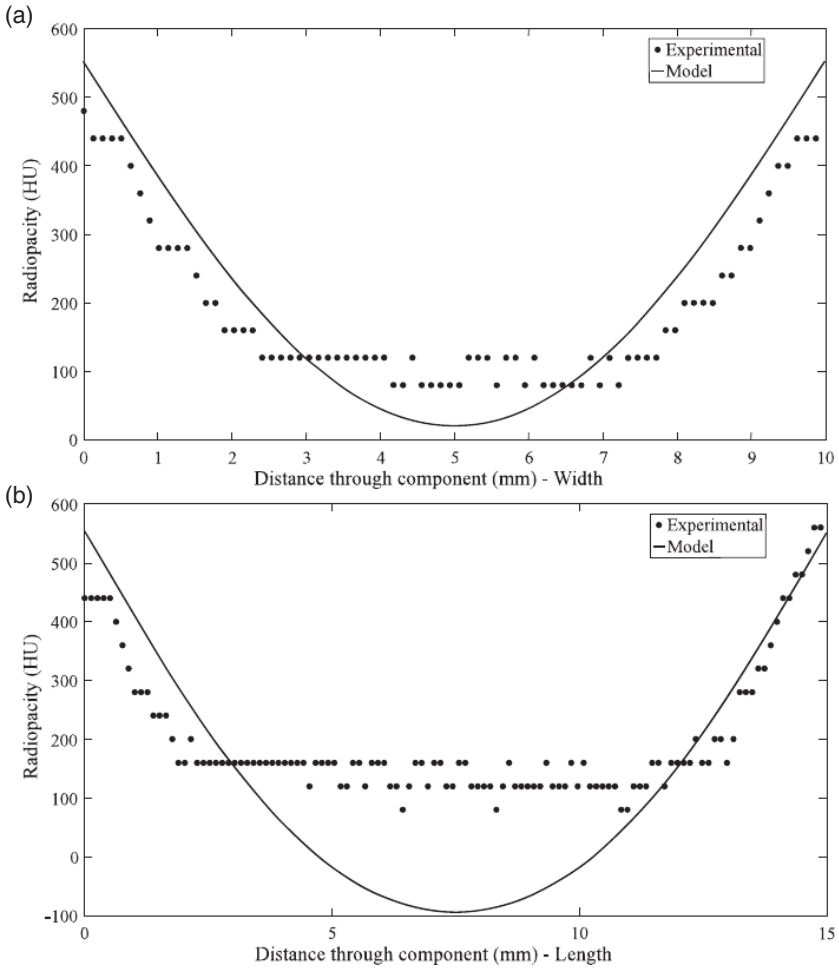

FIGURE 6 The concentration profile for the sample treated at 378 K for 24 h and the 1D model prediction, shown for (a) a profile through the center of the sample width, and (b) a profile through the center of the sample length

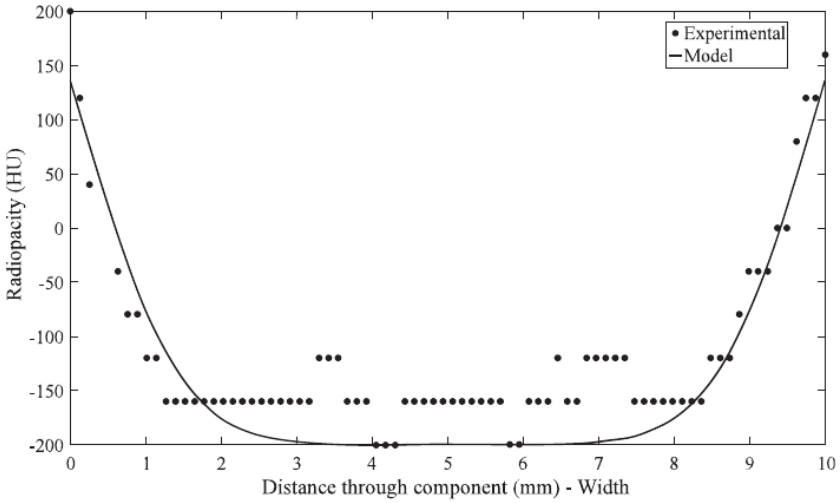

FIGURE 7 The concentration profile for the sample treated at 358 K for 24 h and the 1D model prediction shown for a profile through the center of the sample width

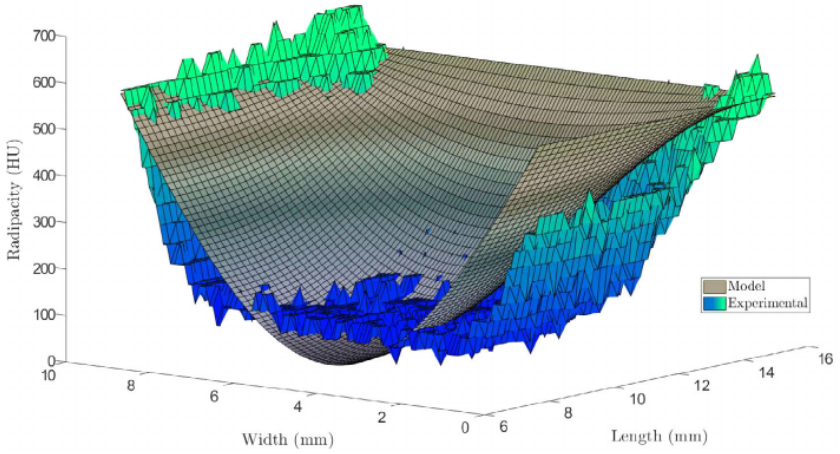

FIGURE 8 The concentration profile across the 2D plane through the thickness of the polyethylene treated at 378 K for 24 h, and the corresponding 2D finite element model prediction [Color figure can be viewed at wileyonlinelibrary.com]

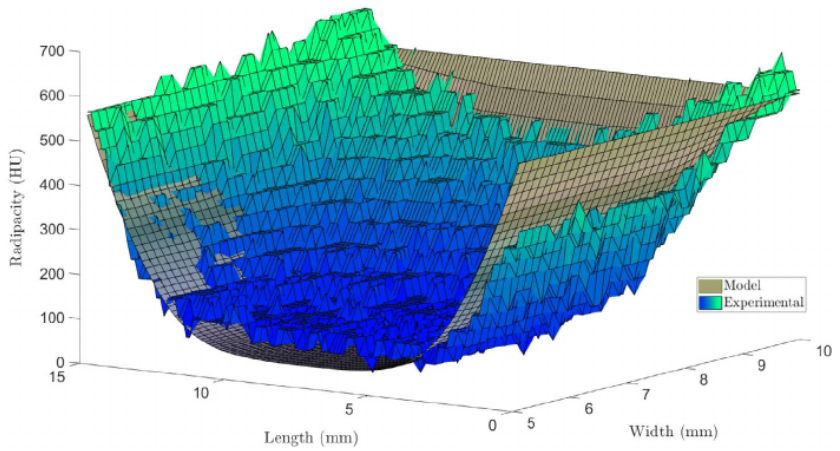

FIGURE 9 Section view of the experimental concentration profile through the 3D volume, showing the results at 2 mm thickness, and the corresponding 3D model data [Color figure can be viewed at wileyonlinelibrary.com]

1D or 2D models, which can be seen visually in Figure 9. The RMSE between the model and the experimental data is summarized in Table 5; for all models the error was higher in the 2D model compared to the 3D. However,

TABLE 5 The RMSE between the predicted radiopacity of the 2D and 3D Fickian-diffusion models and the experimental data for different treatment conditions

Temp (K)	Time (h)	Model	RMSE (HU)
358	12	2D	118.2
		3D	104.0
358	24	2D	112.3
		2D	106.4
378	12	2D	190.6
		3D	160.4
378	24	2D	185.1
		3D	172.0
398	12	2D	662.6
		3D	653.8
398	24	2D	558.4
		3D	514.6

Abbreviations: HU, Hounsfield units; RMSE, root mean square error.

the error of the 398 K condition was particularly high, more than three times that of the other temperatures.

3.5 | Diffusion model fitting

In the final stage of model development, the best fit for the model and the experimental data for cuboid data was identified. The model was fit firstly by just varying the diffusion coefficient, and then second by allowing both the diffusion coefficient to change and the surface concentration within a set boundary of realistic experimental error (±40 HU). The results of these two approaches are shown in Figure 10 and it can be seen that the second approach achieved the closest match to the experimental data.

3.6 | Validation

The optimally fitted 3D model was then applied to two new geometries to assess the accuracy of the model; dogbone-shaped samples, and a knee replacement

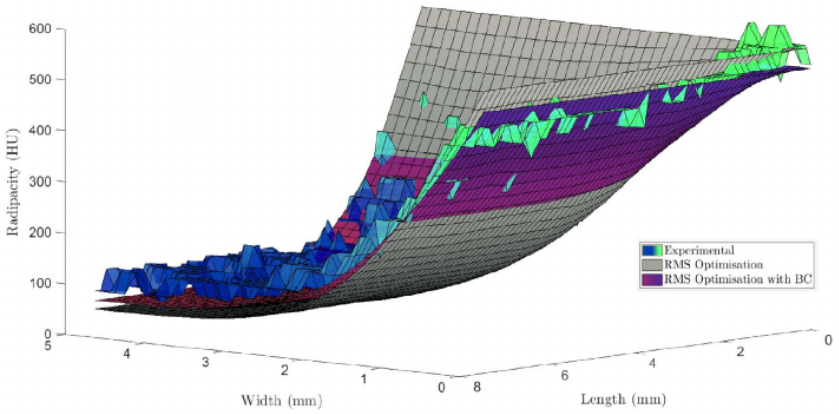

FIGURE 10 Quarter section of the radiopacity predicted by the fitted Fickian-diffusion model with "fixed" and "variable" boundary condition compared to the experimental data at 2 mm slice thickness, for the 398 K 24 h condition [Color figure can be viewed at wileyonlinelibrary.com]

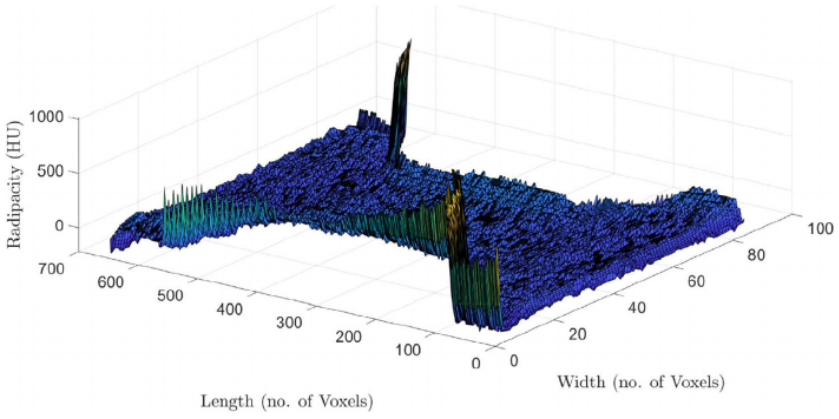

FIGURE 11 Plot of the difference between the model and experimental data in Hounsfield units (HU) through a central slice of the dogbone sample, diffused at 358 K for 24 h [Color figure can be viewed at wileyonlinelibrary.com]

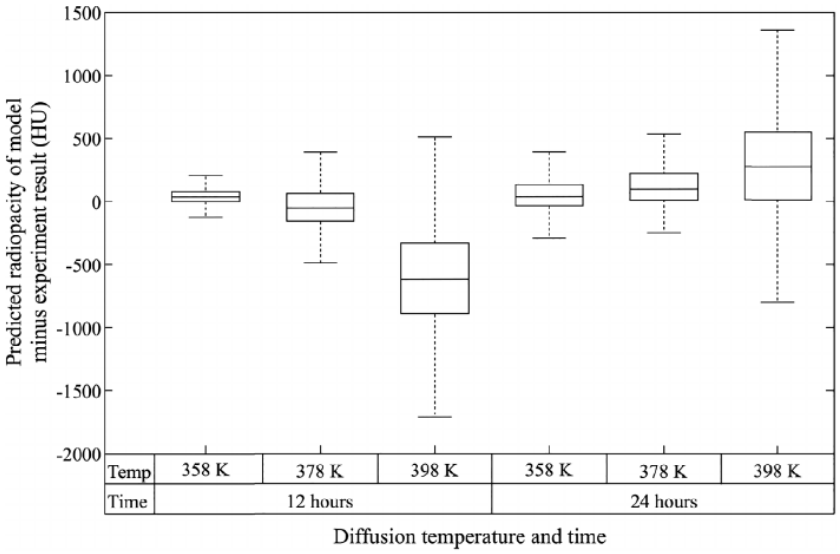

FIGURE 12 Difference between the predicted radiopacity throughout the dogbone volume and the experimentally measured radiopacity, for different temperature and time conditions (outliers 1.5 x interquartile range removed). Results shown are for all voxels within the dogbone

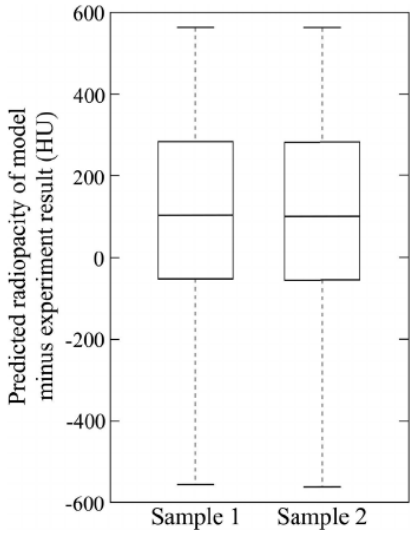

FIGURE 13 Difference between the predicted radiopacity of the Oxford partial knee bearing from the optimized 3D model, and the experimentally measured radiopacity, for two Oxford partial knee bearings immersed for 24 h in Lipiodol at 378 K. Results shown are for all voxels within the bearing

bearing. For the dogbone-shaped samples the 3D model fit the data well, with spikes of large error at the outer surface (Figure 11). For dogbone samples treated at 358 and 378 K for both 12 and 24 hours, the median error was comparable (358 K 12 h:50 HU, 378 K 12 h:-49 HU, 358 K 24 h:49 HU, 378 K 24 h:116 HU) and appeared to be random rather than systematic (Figure 12). The interquartile range was on average 170 HU, representing approximately 20% of the overall radiopacity range for the dogbone samples. When the spikes in the data were removed this reduced to 7% inaccuracy. A much greater error was observed for the samples treated at 398 K, where the model at 12 h underestimated the radiopacity by 608 HU, and at 24 h overestimated the radiopacity by 284 HU. Furthermore, the distribution of error between the model and the experimental data was much wider, and comprised approximately 50% of the overall radiopacity.

The model was also validated against Oxford Partial Knee bearings (highly cross-linked polyethylene). The model was able to predict the general trend of diffusion; but unlike dogbone samples the model had a systematic bias and consistently overestimated the radiopacity by approximately 100 HU (Figure 13). The interquartile range for the two samples was 562 HU and 540 HU, which was on average 97% of the overall radiopacity range for the samples.

4 | DISCUSSION

This study aimed to develop an FE model, which can predict the diffusion of oil-based fluids into semicrystalline polymers using the simplest possible method for practicality. The system of Lipiodol diffusion into polyethylene was used, and the experimental behavior of Lipiodol diffusion showed a Fickian-type diffusion. This information can assist with the manufacturing process to reduce the overall cost by accurately controlling the temperature and time duration.

Most diffusion models for polymers (Crank history-dependent model, Oral model) assume that the surface

concentration instantaneously reaches its maximum value[13,15] and varies with temperature. The results of this study confirmed that the surface concentration of Lipiodol in polyethylene exponentially increased with temperature. Oral et al. observed the same relationship for the surface concentration of Vitamin E diffused into UHMWPE.[6] So the models performed in this work assumed that the surface concentration for a given time period was reached instantaneously, but that the maximum surface concentration was particular to a certain temperature. For example, at 398 K when samples treated for 24 h the surface concentration was set at 2322 HU for the entire time period, whereas in modeling an equivalent 12 h sample the surface value was set at a lower 1386 HU for the entire duration.

One possible reason for the alteration of surface concentration with time and temperature could be the limited resolution of the scanner, so it is not necessarily feasible to measure the true radiopacity at the outer surface. However, the consistency and magnitude of the difference suggests otherwise and indicates that the surface concentration most likely changes with temperature, and may change dynamically with time. The Long and Richman model[14] has a time-dependent surface concentration, and this may be a more realistic representation of the true diffusion profile.

The diffusion coefficient also showed to vary with time and temperature. Understanding and correctly representing a time-dependent diffusion coefficient is complex and requires a large set of experimental results and time points.[16]

However, the complex microstructure of semicrystalline polymers is another possible reason for the variation observed in the saturation surface concentration. In a semicrystalline polymer, diffusion is primarily restricted to the amorphous regions[6] as the crystalline regions have been shown to hinder the diffusion of molecules.[17] To obtain enough oil throughout the samples, an elevated temperature is required and this increases the mobility of the molecular chains and this is likely to increase the permeability of the crystalline regions, thereby increasing the diffusion rate.

Another possible explanation which would result in a time-dependent diffusion coefficient is that the diffusion coefficient is directly dependent upon the concentration of Lipiodol, perhaps because the Lipiodol itself acts as a plasticizer and increases the mobility of the molecular chains, therefore indicating the need for a concentration-dependent diffusion coefficient as referred to by Crank.

Furthermore, the properties and nature of oil at varying temperatures should also be considered. The diffusion coefficient is highly affected by the size and the shape of the diffusant.[18] Lipiodol contains chain fatty acids with different lengths and most likely for an accurate representation, multiple diffusion coefficients are required. In addition, the viscosity of the oil changes with temperature altering the flow properties, so this can suggest the diffusion coefficient is not constant through the whole experiment.[19]

The optimisation algorithm was used to mitigate the effect of these multiple unknown experimental variables. The results of this study clearly demonstrate that to utilize a 1D or 2D Fickian model to represent the oil-polyethylene diffusion system (such as the model used by Oral et al.[6]) introduces significant error in the center of the sample, so a 3D model is essential for accurate representation of the diffusion throughout the volume. Without the fitting, the 3D model had low error at 358 and 378 K, but exceeded 500 HU at 398 K.

The final model was validated on different geometries (dogbone shaped and Oxford Partial Knee mobile bearing knee). It was observed that the accuracy of the model decreased as the temperature increased, perhaps suggesting that the Fick's model is too limited to account for the thermally dependent properties of a semicrystalline polymer.

The fitted model represented the general trend of diffusion correctly for the dogbone and Oxford Partial Knee bearing samples; however, the Oxford partial knee bearing models had a high error and consistently overestimated the radiopacity. The more complex geometry of the knee bearings could be a possible explanation for the difference between the model and the experimental results. Another possible reason is that the model was fit to data from an uncross-linked polyethylene, and the Oxford Partial Knee bearings had been cross-linked as part of their manufacture, which changes the internal structure of the polymer and can hinder the pathway of diffusion. Cross-linking is common for medical application of polyethylene but it is not always necessary. This study provides a general avenue for the predication of diffusion in polyethylene for both medical and nonmedical applications. The limitations of Fick's laws in representing the diffusion of oil in polyethylene, particularly at high temperatures, have been demonstrated, and highlight the need for a time/temperature dependent surface concentration and perhaps a concentration-dependent diffusion coefficient for a representative model.

5 | CONCLUSIONS

The ability to predict the oil distribution within polyethylene from different time and temperature conditions could greatly assist with manufacturing planning for oil-infused polyethylene parts. The 1D and 2D diffusion

models were unable to fully represent the diffusion observed experimentally, but the 3D Fickian model was able to predict the spatial distribution of oil within the polyethylene without systematic error. To our knowledge, the 3D model is one of the most accurate representations of this complex system, and for lower temperatures (358 and 378 K) the root mean squared error was 7.2%. Overall, it was concluded that although other factors such as the degree of crystallinity and the chemistry of the oil should be considered to enhance the fidelity of the model, this study shows that 3D simulation should be an essential part of any future diffusion model of oil within polyethylene.

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5.2 Summary

The research in this chapter explored the potential of using Fick's law of diffusion to predict the Lipiodol concentration within the polyethylene after treatment. The goal of the study was to identify an accurate but also simple model to facilitate manufacturing decisions for optimal treatment of different part geometries. The key findings from this chapter are summarised below.

- The model was only able to represent the distribution of oil within the polyethylene geometries when a 3-dimensional model was used. The 1-dimensional and 2-dimensional models both underestimated the diffusion in the centre of the samples, as was observed for Oral's model of vitamin E polyethylene[46]. The 3-dimensional model was able to predict the Lipiodol concentration to within 20% of its true value throughout the volume, highlighting the importance of using 3D model for manufacturing planning.

- The accuracy of the model was reduced at higher temperatures and it was concluded that this was due to the effect of temperature on the internal structure of polyethylene. The thermal dependence of the polyethylene, and possibly the oil, as well as the semi-crystalline nature of the polyethylene creating regional variation in permeability, creates a very complex set of diffusion conditions which could not be represented using Fick's law.

- All the models were able to confirm the general profile of diffusion suggesting that Fick's law of diffusion is an appropriate starting point, and is sufficient for providing manufacturing treatment parameters for different parts. Future work should evaluate other non-Fickian models such as free volume theory.

Chapter 6

Chemical stability of oil-infused polyethylene

6.1 Context

As explained in Chapter 2 and 3 oxidation of polyethylene is a major clinical concern; and due to the presence of free radicals within the polyethylene generated during the polymerisation, polyethylene is always susceptible to oxidation. Numerous studies on retrieved implants have showed evidence of oxidation and oxidative wear. The literature review provided in Chapter 2 discussed ways that different manufacturers have tried to address the issue of polyethylene oxidation; however, they have not always been successful.

For example, Crossfire polyethylene (Stryker Orthopaedics, Mahwah, New Jersey) was launched in 1998 as a new polyethylene with superior wear resistance. Crossfire polyethylene was irradiated with a high dose to maximise crosslinking and improve wear properties. One of the consequences of the irradiation is that it further increased the number of free radicals within the polyethylene, so to address this an annealing step was added where the polyethylene was held just below the melting point with the intention of neutralising the majority of the free radicals. Although the annealing process did reduce the number of free radicals, it did not remove them all and *in-vitro* studies showed the free-radical concentration in Crossfire polyethylene was twice as high as that of standard sterilised polyethylene. Clinical evaluation showed severe signs of oxidation and fatigue damage in less than 4 years[91], and retrieval analyses showed that seven out of twelve acetabular cups exhibited severe oxidation with white bands, pitting and delamination (Figure 6-1).

The initial mechanical testing of Crossfire had promising results, and showed a higher yield and ultimate tensile strength compared to standard crosslinked polyethylene. However, later accelerated ageing studies showed a significant increase in crystallinity (from 58% to 65%) of

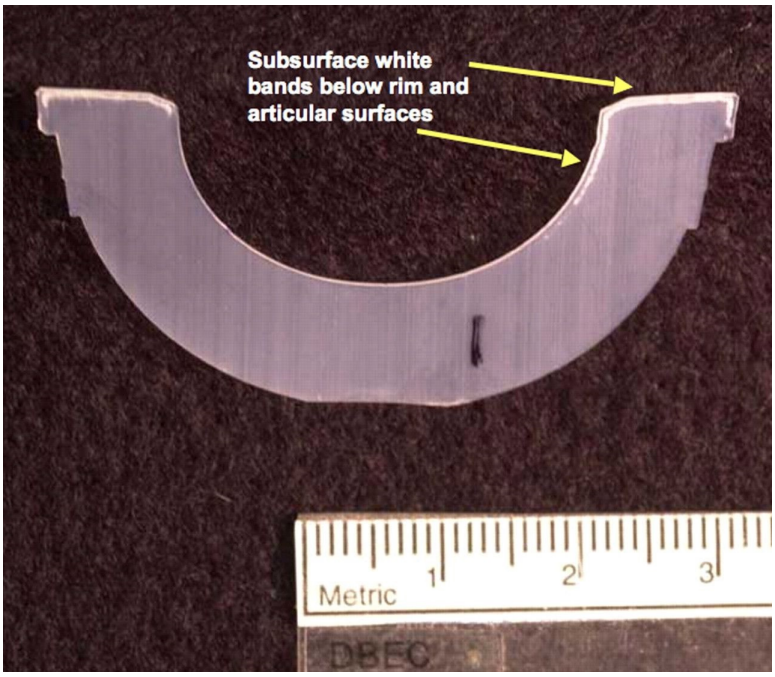

Figure 6-1: Photograph of a Crossfire acetabular cup retrieved after 3.3 years of implantation showing evidence of severe oxidation, with a subsurface white band on the rim and also on the articular surface[92].

the polyethylene. The case of Crossfire highlights the importance of considering the oxidative stability of polyethylene and to simulate the *in vivo* conditions as well as possible prior to clinical use[47].

In the first part of the paper in this final chapter, the oxidative stability of polyethylene was studied using an accelerated ageing method. The second part of the study quantifies the leaching of Lipiodol from the polyethylene samples and compares it with the leaching of vitamin E, as a clinically used control. The radiopaque polyethylene could lose its functionality due to the leaching of Lipiodol and even though the contrast agent is FDA approved there may also be safety concerns; hence, it is important to examine the leaching to plan the design and the duration of the part's functionality.

Appendix 6B: Statement of Authorship

This declaration concerns the article entitled:			
Oxidative and Chemical Stability of Polyethylene is Enhanced by Oil Infusion			
Publication status (tick one) **Draft manuscript** [ ] **Submitted** [ ] **In review** [ ] **Accepted** [ ] **Published** [x]			
Publication details (reference)	Zaribaf, F. P., Gill, H. S., & Pegg, E. C. Journal of Biomaterials Applications (2020). DOI: 10.1177/0885328220977353		
Copyright status (tick the appropriate statement) I hold the copyright for this material [ ] Copyright is retained by the publisher, but I have been given permission to replicate the material here [x]			
Candidate's contribution to the paper (provide details, and also indicate as a percentage)	The candidate considerably contributed to the The candidate contributed to the "**Formulation of ideas**", alongside the co-authors The candidate considerably contributed to the "**Design of methodology**": The candidate designed the methodology based on the knowledge available in the literature and the co-authors revised the proposed methodology and proposed amendments to improve the design The candidate conducted the "**experimental work**" under the supervision of Dr Elise Pegg The candidate considerably contributed to the "**presentation of data in journal format**": The candidate drafted the original manuscripts which has been revised by all the co-authors. Dr Elise Pegg significantly contributed to improve the quality of the manuscript and assisted with data visualisation.		
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.		
Signed	F.Zaribaf	**Date**	27/11/2020

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Chemical stability of oil-infused polyethylene

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Abstract

Ultra-high molecular weight polyethylene (UHMWPE) can be made radiopaque for medical imaging applications through the diffusion of an iodised oil-based contrast agent (Lipiodol Ultra Fluid). A similar process is used for Vitamin E incorporated polyethylene which provides antioxidant properties. This study aimed to investigate the critical long-term properties of oil-infused medical polyethylene after 4 weeks of accelerated thermal ageing. Samples treated with an oil (Vitamin E or Lipiodol) had a higher oxidation stability than currently used medical grade polyethylene, indicated by a smaller increase in oxidation index after ageing (Vitamin E +36%, Lipiodol +40%, Untreated +136%, Thermally treated +164%). The tensile properties of oil treated polyethylene after ageing were significantly higher than the Untreated and Thermally treated controls ($p>0.05$) indicating less mechanical degradation. There was also no alteration in the percentage crystallinity of oil treated samples after ageing, though the radiopacity of the Lipiodol treated samples reduced by 54% after ageing. The leaching of oil with time was also investigated; the leaching of Lipiodol and Vitamin E followed the same trend and reached a steady state by two weeks. Overall, it can be concluded that the diffusion of an oil-based fluid into polyethylene not only increases the oxidative and chemical stability of polyethylene but also adds additional functionality (e.g. radiopacity) providing a more suitable material for long–term medical applications.

Keywords

Medical polyethylene. Antioxidant. Radiocontrast. Thermal ageing. Joint replacment. Mechanical testing.

Introduction

Ultra-high molecular weight polyethylene (UHMWPE) is one of the most common bearing surfaces used in joint replacements. The long-term properties and durability of polyethylene play a significant role in the outcome of the surgical procedure [1,2]. Around 1% of orthopaedic procedures fail within the first 10 years of implantation [3], and most of the material-related failures can be associated with oxidative degradation of the polyethylene. Oxidised polyethylene has a higher brittleness which makes the polymer more prone to crack and wear [4]. Polyethylene wear particles can also trigger bone loss (osteolysis) and lead to issues such as mechanical implant loosening which often require revision surgery [1,5].

Polyethylene has a limited X-ray attenuation making it difficult to see in a radiograph [6]. As a result of its limited X-ray attenuation, clinical evaluation of components and the early diagnosis of failure are challenging. To address this limitation, in our laboratory we developed a radiopaque polyethylene which contains an FDA approved oil-based contrast agent (Lipiodol Ultra Fluid) [7]. Previous work identified an optimal treatment protocol which maintained the mechanical and physical properties of the polyethylene [8]; however, it is critical to assess how these properties will change over the long-term in an *in vivo* environment.

The most common mechanism of polyethylene degradation *in vivo* is oxidation. Oxidation of polyethylene can be explained by Bolland's cycle [10]. In this cycle, the alkyl radicals present in polyethylene (due to the polymerisation and processing) react with oxygen to form peroxy radicals, which are able to attack other polymer molecules to form hydroperoxides and regenerate the original alkyl radicals. Hydroperoxides will eventually decompose to form more stable oxidation products (ketones, second aryl-alcohols, carboxylic acids and esters, see Table 1), which can be

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quantified using Fourier Transform Infrared Spectroscopy (FTIR)[4].

It takes months or years to reach a detectable level of oxidation at ambient and body temperature[11]; this is due to the slow diffusion of oxygen. It takes up to 120 days for an oxygen molecule to move 1 mm below the surface of a crosslinked polymer and for an uncrosslinked sample with 52% crystallinity 100 days is required for oxygen to travel 1 cm (diffusion coefficient 10^{-7} cm^2s^{-1})[12]. Consequently, an accelerated ageing protocol is required to experimentally assess the propensity of a polyethylene to oxidation in a reasonable time-frame[13].

All attempts to accelerate the rate of oxidation of polyethylene to date have either increased the diffusion flux of oxygen at the implant surface, or increased the kinetic rate of oxidation. Both of which can be achieved either by increasing the oxygen concentration at the boundaries (the partial pressure of oxygen in the atmosphere) or by exposing the sample to an elevated temperature. There are two commonly used standardised protocols of thermally accelerated ageing (ASTM F2003-02(2008)); in the first one the specimens are kept for 2 weeks in pure oxygen of 0.5 MPa pressure at 70°C, in an air convection oven. In the second method, all specimens are kept at 80°C at atmospheric pressure for 4 weeks in an air convection oven. Both protocols replicate five years of natural polyethylene ageing *in vivo*[11,15,16]. Recent studies have developed even more aggressive accelerated ageing methods, which make use of squalene to more closely replicate *in vivo* oxidation.[17]

Many clinical and laboratory studies have shown an increase in the crystallinity and a reduction in ductility and toughness of polyethylene after ageing[11], hence it is crucial to also evaluate the mechanical properties and the percentage crystallinity of the aged polymer. Furthermore, it is unknown if the oil content can diffuse out of the polyethylene with time and consequently remove/reduce the intended functionality, such as radiopacity or antioxidant properties.

The aim of this study was to investigate long-term changes in the physical, thermal, chemical and tensile properties of Lipiodol-infused polyethylene, as compared to antioxidant vitamin E infused polyethylene which is used commercially for joint replacement implants.

Materials and methods

The experiments studied the longevity of oil-infused polyethylene by examining the thermal properties (melting point and crystallinity), oxidative stability, mechanical stability, and oil-diffusion stability (leaching) of the polyethylene. For the radiopaque Lipiodol treated polyethylene the radiopacity was also quantified before and after ageing (Figure 1).

Sample Preparation

The polyethylene used in this study was 4 mm thick sheet moulded un-irradiated GUR 1050 UHMWPE with an average molecular weight of 5.5 to 6.0 million g/mol, provided provided by Celanese, Inc (Oberhausen, Germany). GUR 1050 sheets were cut to small cuboids of 10 mm by 10 mm by 4 mm, and tensile test specimens with the geometry specified in ISO 572 Annex A, type 1AB[18].

Four different types of samples were used in this study (Table 2), with five sample repeats of each type. Radiopaque samples were immersed in 25 ml of Lipiodol (Guerbet, France) at 105°C for 18 hours to create Radiopaque polyethylene[19]. The second group of samples were immersed in 25 ml of Vitamin E (L-α–tocopherol, Sigma-Aldrich, Kent, UK) at 105°C for 18 hours to create the Vitamin E samples. Thermally treated samples were treated at the same elevated temperature and time (105°C for 18 hours) without the presence of any oil; and finally the Untreated control samples were not treated with temperature or any oily fluid.

At the end of the treatment time, the samples were allowed to cool down to ambient temperature and wiped with a lint-free tissue to remove any excess oil from the surface.

Accelerated Ageing

The accelerated ageing protocol used in the current study was in accordance of ASTM F 2003-00[13]. All the prepared samples were kept in the oven for 4 weeks at a constant temperature of 80±2°C[11] and the material properties were assessed before and after ageing.

Leaching

In vitro leaching of oil was evaluated in two different solutions: saline solution and Dulbecco's Modified Eagle's Medium (DMEM); both purchased from Sigma-Aldrich (Kent, UK). Penicillin-Streptomycin (Sigma-Aldrich, Kent, UK) was added to the DMEM solution (0.2% v/v) to prevent any bacterial growth. Each sample was located in a separate well (n=5) and immersed in 10 ml of one of two solutions. The solutions were topped up every two days to mitigate the effect of evaporation. All the samples were located in an incubator (Incu-50S, SciQuip, UK) with a control

Table 1. Different species and products are involved in the oxidation of polyethylene; each of these products can be identified from FTIR spectra[4,14], with the exception of radical species. NA=not applicable.

Oxidation step	Oxidation by-product	Representative peak position (cm^{-1})
Active species causing oxidation	Alkyl radicals	NA
	Trans-vinylene group (RCH=RCH)	964
Reactants and intermediate products	Trans-vinylene group (RCH=RCH)	964
	Alkyl radicals	NA
	Allyl radicals	NA
	Polyenyl radicals	NA
End products	Water	3410
	Hydroperoxides	3550
	Carbonyl groups (aldehydes and ketones)	1718
	Alcohol groups	3410
	Branches and crosslinks (including O-O bridges)	800-1000
	Ester	1741
	Carboxylic acids	1713
	Additional methyl groups	1378

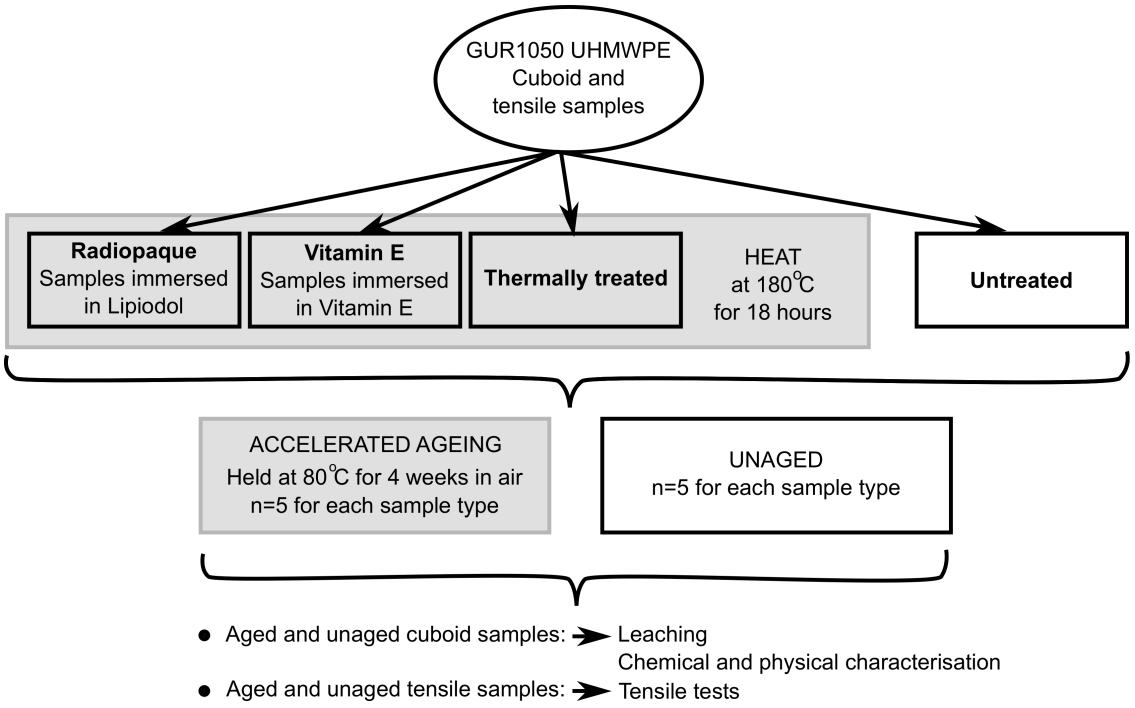

Figure 1. A schematic of the experimental procedure

Table 2. Treatment conditions and additives used to prepare the four different sample types analysed. NA=not applicable.

Sample type	Treatment condition	Additive
Radiopaque	Held at 105°C for 18 h	Lipiodol
Vitamin E	Held at 105°C for 18 h	Vitamin E
Thermally treated	Held at 105°C for 18 h	NA
Untreated	NA	NA

temperature of 37°C. The leaching was quantified from the gravimetric changes.

Crystallinity Measurement

Differential scanning calorimetry (DSC 250, TA Instrument, Delaware, United States) was used to determine the melting point and the degree of crystallinity of UHMWPE (n=5). Approximately 2.0 mg of each sample was taken from the outer surface of the samples to be analysed with DSC. The pan was crimped with an aluminium cover. The testing processed from 20°C to 180 °C at a heat flow of rate 10°C/min under a nitrogen purge. TA Instruments Universal software (Version 4.5) was used to analyse the data and calculate the degree of crystallinity. The crystallinity was

calculated by first integrating the endothermic peak from 50°C to 160°C to find the enthalpy of fusion of the sample, and then by normalising the enthalpy of fusion with the heat of fusion (289 J/g[21]).

Radiopacity Measurements

All the Radiopaque samples were imaged using a μCT scanner (X Tec, XT H 225 ST, Nikon Metrology UK Ltd, Derby, UK) before and after the ageing process; scanning protocols were the same for all samples (162 kV, resolution 0.2 mm). Analysis of the CT data was performed using Simpleware ScanIP (Synopsys Inc., Exeter, UK release version 2017). Water and air were used for calibration to calculate the Hounsfield units (HU)[22].

Gravimetric Changes

The weight of all samples was measured using a digital scale (Model XP205, Mettler Toledo, Columbus, OH, USA) before and after the sample preparation treatment, the accelerated ageing, and the leaching experiment. The Lipiodol intake and leaching was calculated from this information. For the leaching investigation, the gravimetric change in the samples was measured at weeks 0, 1, 2, 4, and 8.

FTIR

A thin slice (approximately 200 μm) was sectioned from the surface of each cuboid sample using a sledge microtome. A Thermo Scientific spectrometer (Nicolet 560, Thermo Fisher Scientific, Waltham, MA, USA) was used to obtain the FTIR spectra in transmission mode. An average of 32 scans was taken for each section from 4000 to 600 cm^{-1}. FTIR spectra was collected from each specimen within 24 hours of the start and end of accelerated ageing. Peaks to identify oxidation and crystallinity content were the interest of this study.

The oxidation index was calculated based on ASTM F2759–19[23]. The area under the carbonyl peak (1740 cm^{-1}) was normalised against the peak from the methyl stretch at 1370 cm^{-1}. Lipiodol contains iodine, and the presence of an electronegative group can shift the peak by 15 cm^{-1} [24], hence shifted peaks were used for the Radiopaque samples.

Tensile Mechanical Testing

Tensile tests were conducted at room temperature in accordance with ISO-527[18] using an electromechanical test machine (Model 5965, Instron, Norwood, MA, USA) at a rate of 50 mm/min. The tests were carried out with aged untreated UHMWPE, aged thermally treated UHMWPE, aged Vitamin E UHMWPE and aged Radiopaque UHMWPE. Five specimens per condition were tested to calculate the tensile modulus (E), 0.2% yield strain, ultimate tensile strength (UTS) and elongation at failure. The raw data were processed by a custom MATLAB script (R2017a, The MathWorks Inc., Nattick, MA, USA). The calculations were conducted as specified in the standards[18].

Statistical Analysis

A Kruskal-Wallis test was used to compare the experimental results between different sample groups, and Mann-Whitney U tests were performed to compare the results of each sample group before and after ageing. IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) was used to perform the statistical analysis. The statistical differences in the above comparisons were considered significant at the $p<0.05$ level.

Results

Accelerated Ageing

The aged Radiopaque samples had lower surface radiopacity compared to the radiopacity of the unaged samples (Figure 2, 54±8% reduction). In the unaged samples the maximum radiopacity observed on the surface of the samples and was 1060±53 HU) and after ageing the surface radiopacity reduced to 600 ±45 HU).

The ageing process had no effect on the percentage crystallinity or melting point of any of samples (Figure 3); and all the p-values were between p=0.055 to 0.51 using Mann-Whitney U tests. The ageing process also did not cause any visible colour change.

The oxidation index of all polyethylene samples increased after ageing. Before ageing, Vitamin E treated samples showed the lowest level of oxidation index (0.274±0.036) while the Radiopaque samples had the highest amount of oxidation (0.796±0.059). However, as Figure 4 shows the increase in the oxidation index of the Radiopaque samples after ageing was much lower than the Thermally treated and Untreated samples ($p<0.005$). The oxidation index of the Untreated and Thermally treated samples increased by 50% and 115% respectively after ageing, and the oxidation index of the Radiopaque and Vitamin E treated samples increased by 36% and 24% respectively.

There was no evidence of ketone (oxidation by-product) present in any of the FTIR spectra (peak at 1718 cm^{-1}) before ageing, however after ageing, the ketone absorbance

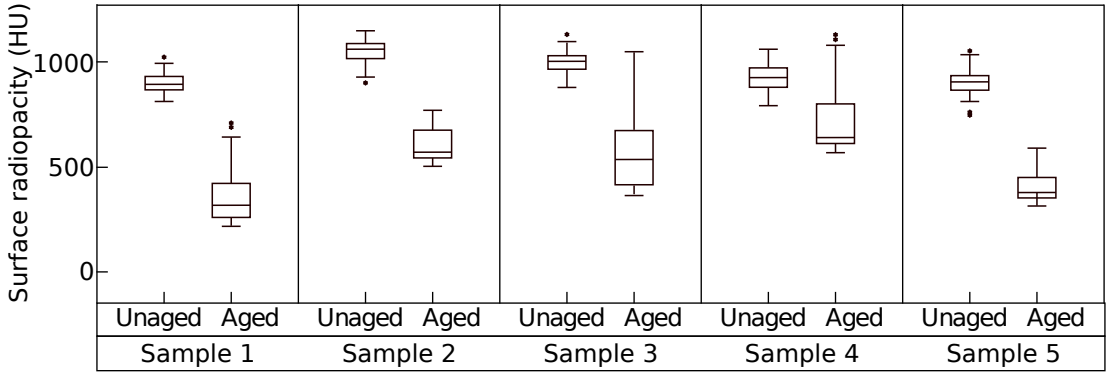

Figure 2. Box and whisker plots of the surface radiopacity to a 2 mm depth of the 5 Radiopaque sample repeats calculated before and after ageing.

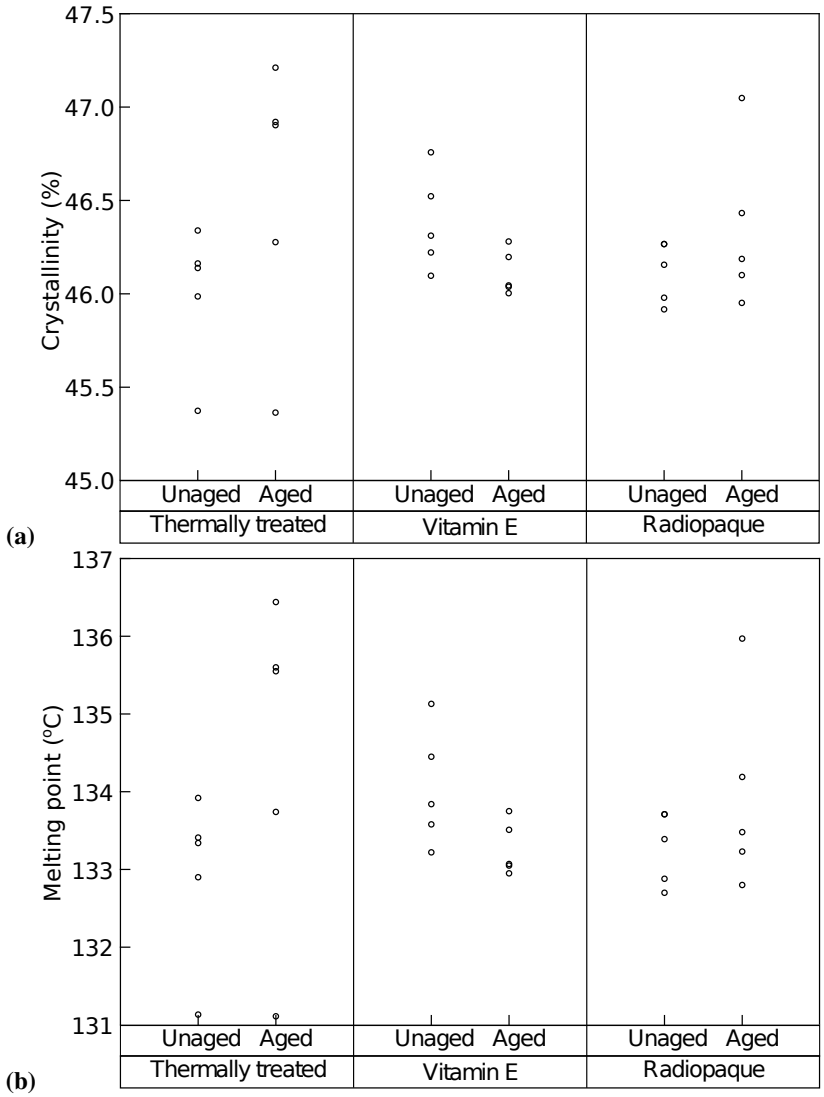

Figure 3. The DSC results indicated no significant ($p>0.005$) alteration in a) crystallinity or b) melting point of any of sample group after ageing

peak was present in the all the spectra, indicating oxidation. Oxidation also leads to formation transvinylene groups and it was observed that the peak for transvinylene groups increased while the vinyl groups peak decreased. Table 3 summarises the peak changes in the sample groups before and after ageing.

The ageing process also led to a significant alteration in the tensile properties of samples. Oil free samples were oxidised

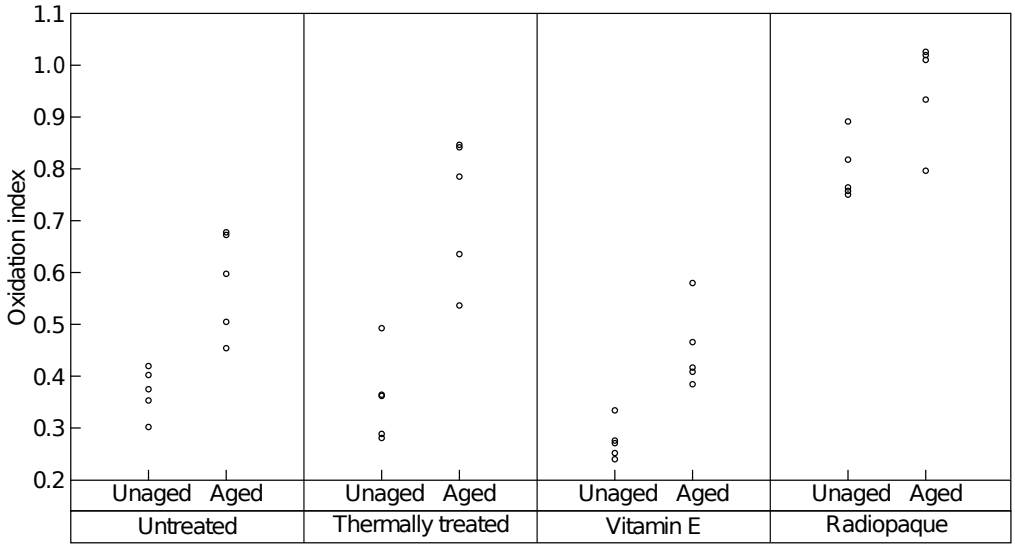

Figure 4. The oxidation index of all the samples increased after ageing. The lowest oxidation index was reported for Vitamin E infused samples whilst the highest was seen in the Radiopaque polyethylene samples.

Table 3. The peaks present in the FTIR spectra for each sample after and before ageing related to oxidation, and the oxidation index (OI) calculated as specified in ASTM F2012-01. ✓=peak present, SD=standard deviation.

Sample	Carbonyl group (aldehydes and ketones)	Hydroperoxides and alcohols	Ester	Trans-vinylene group	Oxidation index (mean±SD)
Untreated Unaged	-	-	-	-	0.345±0.057
Untreated Aged	✓	✓	-	✓	0.518±0.099
Thermally treated Unaged	-	-	-	-	0.344±0.105
Thermally treated Aged	✓	✓	-	✓	0.729±0.137
Vitamin E Unaged	-	-	-	-	0.274±0.036
Vitamin E Aged	✓	-	-	✓	0.451±0.778
Radiopaque Unaged	-	-	✓	-	0.796±0.059
Radiopaque Aged	✓	-	✓	✓	1.01±0.060

and flaky after ageing, and the modulus was on average 84% lower than before ageing (Figure 5a), and the elongation at failure was 67% lower (Figure 6a). The yield strength of the Thermally treated and Untreated samples was higher than the rest of the samples (Figure 5b); however the difference was not statistically significant ($p<0.05$). In terms of ultimate tensile strength (UTS) there was an increase in the UTS of the samples after the ageing process (Figure 6b). The UTS of the Radiopaque and Vitamin E samples was also higher than the Untreated and Thermally treated samples ($p=0.004$). Finally the presence of the oily fluid preserved the ductility of the samples; the elongation at failure of the Radiopaque and Vitamin E samples was significantly higher than Untreated and Thermally treated samples after ageing.

Leaching

Over the first 2 weeks of leaching there was a relatively large decrease in the weight of the both the Radiopaque and Vitamin E polyethylene samples (Figure 7). The average leaching rate for the Radiopaque samples in DMEM was 0.0022±0.008 g/day in the first two weeks. Even though the plot suggests a slightly higher weight reduction for the Radiopaque samples (-0.03 g weight change compared to -0.02g at 14 days), the difference was not statistically significant ($p=0.2$ for DMEM). The weight change of the Radiopaque samples in saline was higher than the Vitamin E samples ($p=0.01$). Table 4 shows the rate of leaching after two weeks and at 8 weeks for each sample group. There was no alteration in the weight of the control samples. After the second week, all samples had reached a steady state weight change of 0.02±0.0001 g/day for both the Radiopaque and Vitamin E samples.

Discussion

This study aimed to evaluate the longevity of oil infused polyethylene (Lipiodol and Vitamin E) by examining how the thermal properties, oxidative stability, tensile properties, radiopacity and oil-diffusion stability might be affected by long-term implantation. The inclusion of an additive, such as Lipiodol for radiopacity or Vitamin E for oxidative stability,

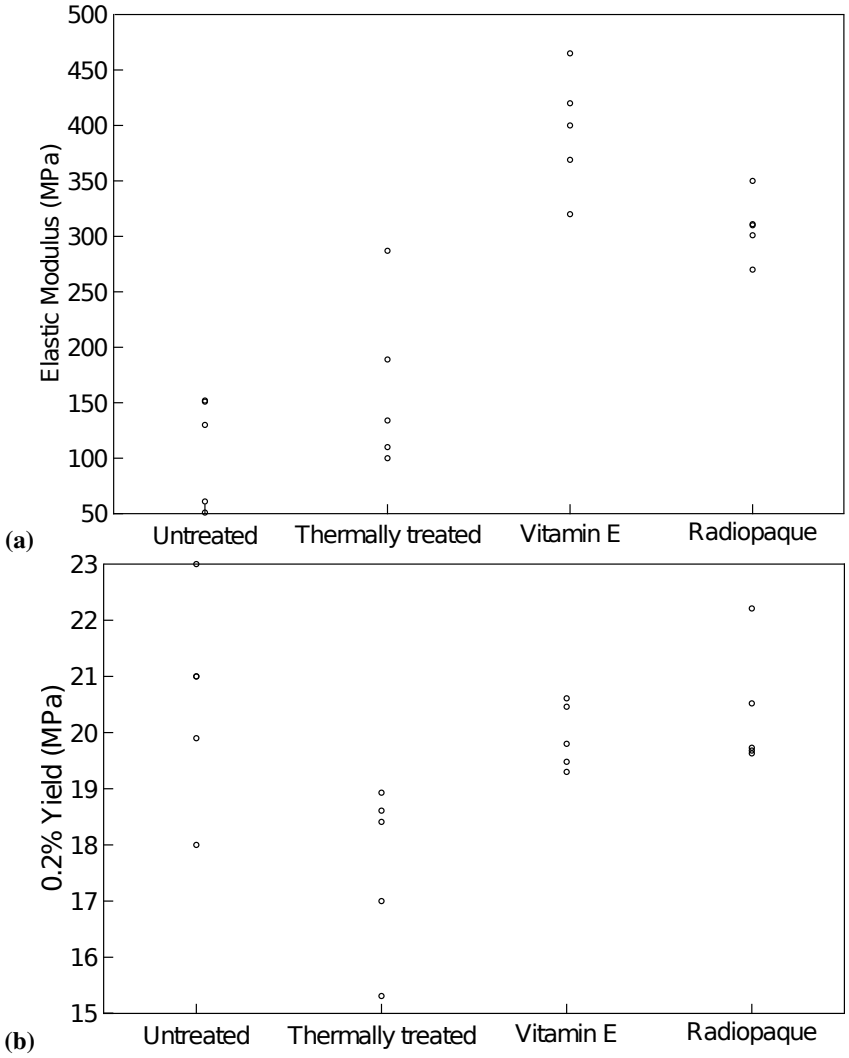

Figure 5. The elastic mechanical properties of oil treated polyethylene; (a) elastic modulus (b) and yield strength. The modulus and yield after ageing of the oil treated samples (Radiopaque and Vitamin E) were significantly higher than the thermally treated and untreated controls (modulus:p=0.56, yield: p=0.006).

Table 4. The average rate of leaching of Lipiodol or vitamin E out of the polyethylene samples at 2 and 8 weeks in saline or Dulbecco's Modified Eagle's Medium (DMEM). SD=standard deviation.

Sample	Leaching rate after 2 weeks (g/day, mean±SD)	Leaching rate after 8 weeks (g/day, mean±SD)
Vitamin E in DMEM	0.0014 ±0.002	0.00034±0.6
Vitamin E in saline	0.0013±0.002	0.00030± 0.3
Radiopaque in DMEM	0.002± 0.007	0.00048± 0.4
Radiopaque in saline	0.002± 0.004	0.00050±0.3

can improve the clinical performance of the polyethylene, but it is important to ensure (a) the functionality is maintained over the implant life and (b) the safety and performance of the material is not compromised.

Lipiodol infused radiopaque polyethylene has an enhanced X-ray attenuation due to the presence of an FDA approved oil-based contrast agent (Lipiodol)[6]. This study showed that the surface radiopacity of aged radiopaque polyethylene samples was on average 54% lower than unaged radiopaque polyethylene. One possible explanation is that the ageing process allowed Lipiodol to diffuse further into the polyethylene away from the surface leading to a homogenised radiopacity and a lower surface radiopacity. The use of thermal treatment to cause homogenisation of oily fluids in polyethylene is deliberately performed for Vitamin E polyethylene to ensure the antioxidant properties protect the whole part[25]. Another possible explanation is that the high temperature led to the oxidation

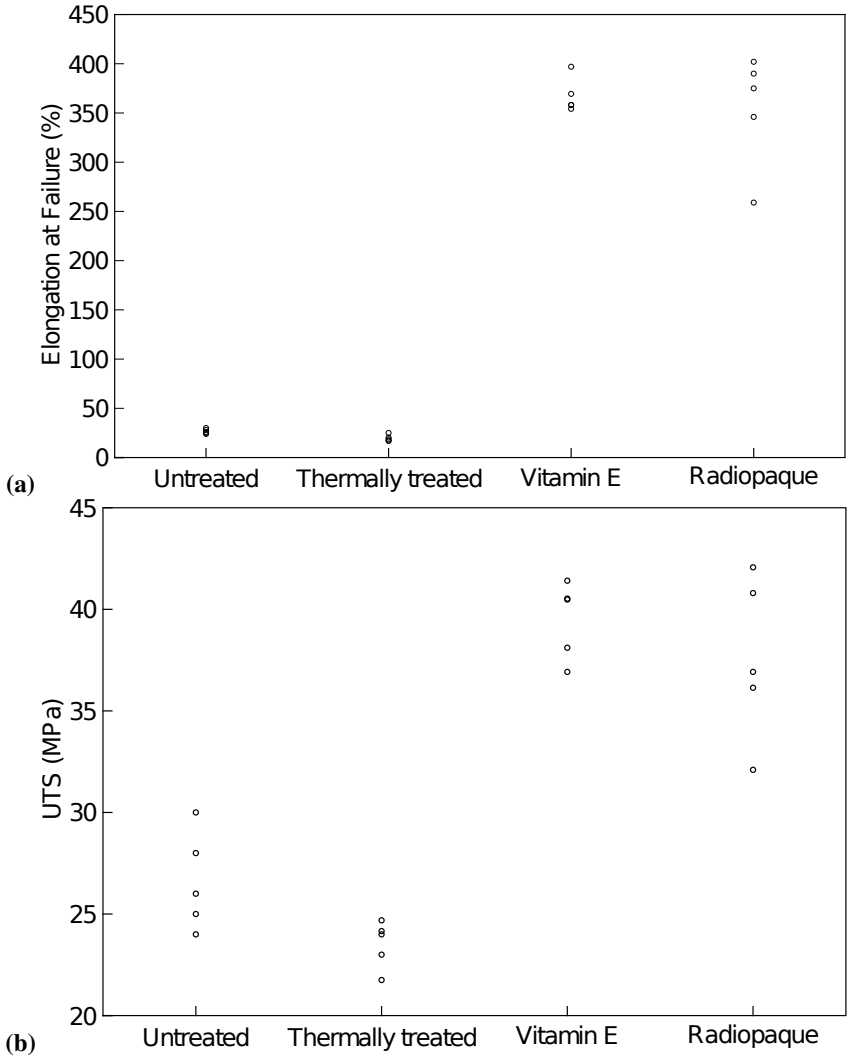

Figure 6. The post-yield mechanical properties of oil treated polyethylene; (a) ultimate tensile strength or UTS (b) and elongation at failure. The UTS and elongation at failure after ageing of the oil treated samples (Radiopaque and Vitamin E) were significantly higher than the thermally treated and untreated controls (UTS: p=0.004, elongation: p=0.002).

of Lipiodol compromising their functionality; there is insufficient data to support this idea however oxidation and degradation of contrast agents with temperature has been previously reported[26–28]. Nuclear magnetic resonance (NMR) spectroscopy scans of aged and thermally treated Lipiodol (unpublished data) show aged Lipiodol contains a higher level of unsaturation compared with unaged Lipiodol; this may reduce the X-ray attenuation of Lipiodol. Unfortunately, the ageing protocol used in this study was designed to replicate the natural ageing of polyethylene and it has not been validated for Lipiodol.

The redistribution of radiopacity can be also associated with the effect of temperature on the crystallinity of polyethylene[19]. The diffusion of macromolecules in polyethylene is limited to the amorphous regions; the elevated temperature and ageing are both likely to cause a decrease in the crystalline regions providing more amorphous regions for Lipiodol to move away from the surface[19]. The degree of crystallinity is one of the most crucial properties of polyethylene. The crystalline content of polyethylene provides an additional resistance to mechanical deformation, so increasing the crystallinity reduces the ductility of the polyethylene[29]. Our previous studies showed that the Lipiodol treatment does not alter the degree of crystallinity of polyethylene[19]. The DSC results (accuracy of $\pm 0.1°C$) from this study also confirmed no significant changes in the crystalline content of the aged samples ($p>0.05$ for all the samples).

The oxidation index of all specimens increased after ageing. Oxidation leads to chain scission and formation of shorter chains[30]; from a thermodynamic point of view, the shorter chains are able to re-arrange themselves into highly crystalline arrangements increasing in the degree of

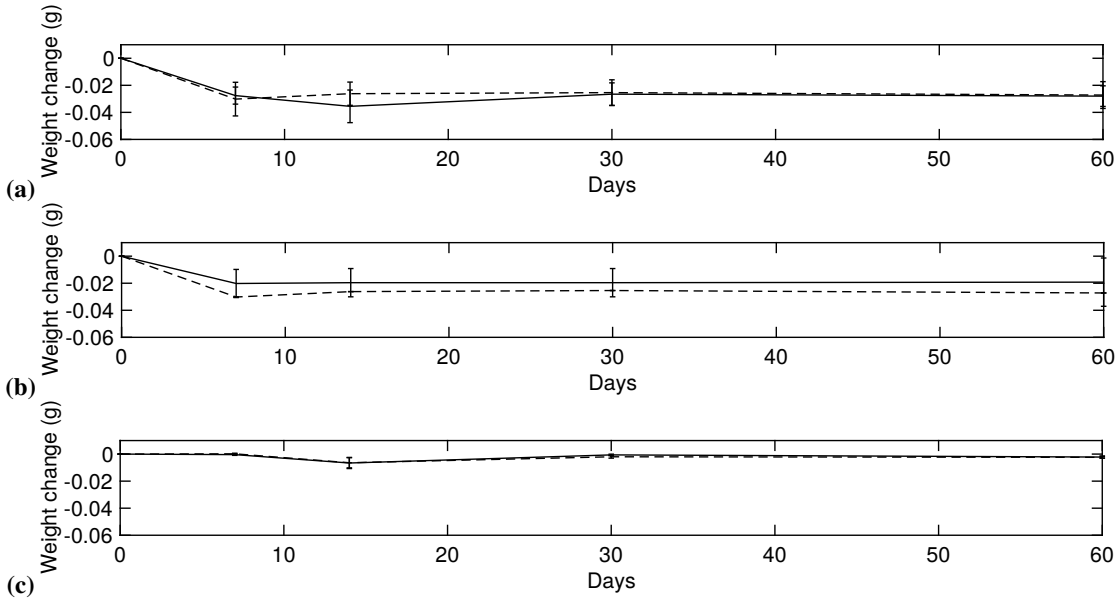

Figure 7. The leaching behaviour of (a) Radiopaque, (b) Vitamin E treated polyethylene samples, and (c) Thermally treated control samples, where the error bar represents the standard deviation. The Lipiodol leaching was slower than the Vitamin E leaching. The control samples were only treated thermally to ensure the the weight change was purely due to the leaching of the oil based fluid in the samples. The dotted lines represent results from samples held in DMEM and the solid lines indicate those in saline.

crystallinity, which contradicts the results from the DSC. The crystallinity can also be examined using FTIR; the peak at 989 cm^{-1} represents the crystalline content of polyethylene and the peak at 1305 cm^{-1} is an identification of the amorphous content of specimens. The FTIR spectra showed that while there was no change in the crystalline peak of the samples before and after ageing, a reduction in the peak at 1305 cm^{-1} indicates a reduction in the percentage of the amorphous phase. This suggests the amorphous regions were transformed into thinner, less perfect crystals, which could not be identified by neither DSC nor FTIR[30]. Previously it has been reported that even though oxidised retrieved polyethylene samples have increased percentage crystallinity, it is uncommon for thermally aged samples to show any significant increase in crystallinity[30,31].

None of the current ageing protocols are able to fully reproduce the oxidative changes seen in naturally aged polyethylene[32]. Natural ageing of polyethylene is affected by multiple factors such as the concentration of free radicals, the duration of shelf storage, the surrounding fluid[16,33] as well as many patient related factors such as lifestyle, level of activity or patients' weight. Previous studies showed that after 4 weeks of accelerated ageing of non-irradiated polyethylene, there were some observations (e.g. ketone peak) which were not associated with long-term naturally aged explants[34].

Although this study showed signs of oxidation after ageing for all samples groups, oil-infused samples showed a superior oxidation stability compared to untreated controls. The increase in the oxidation index of the Radiopaque samples was almost half of the Thermally treated samples and Untreated samples (56% compared to 118%). The Radiopaque samples however had a high initial oxidation index; which may result from the aldehyde peak in Lipiodol which has a similar wavenumber to the peak used to calculate the oxidation index, potentially resulting in an over-estimation of the oxidation index[35]. For a more comprehensive investigation, the peaks representing other oxidation products (e.g. ketone) can be checked. Ketone is one of the common products of oxidation and frequently was found in thermally aged polyethylene[32,34]. None of the specimen groups (including the Radiopaque polyethylene) showed a peak for ketone before ageing, supporting the hypothesis that the high oxidation index of the unaged Lipiodol treated samples was not due to true oxidation but was as a result of a systematic error in the Oxidation Index calculation.

This study also evaluated the effect of oxidation on the tensile properties of polyethylene, the oil-free samples had significantly lower tensile properties (elastic modulus, yield, elongation at failure, $p<0.05$) than any oil treated sample. For instance, the oil-free samples were very brittle and had an elongation at failure less than 50%, while this value for the oil treated samples was more than 300%. The oil free samples also had a lower modulus compared to the oil treated samples. Furthermore, many of the tensile properties of the

Radiopaque samples were on average slightly lower than the Vitamin E samples, yet never statistically significant.

The leaching of Lipiodol was confirmed thorough a reduction in weight after the first measurement at week 2. After week two the rate reached a plateau suggesting minimal further leaching. This could be because fluid on the surface of the samples had diffused through to the centre, away from the surface, and was no longer able to diffuse out due to the very slow rate of diffusion. Neither DMEM nor saline fully represent the synovial fluid; saline does not contain the proteins or lipids and although DMEM has a similar protein content it has no lipid content. However, to our knowledge there is no cost-efficient fluid which fully represents synovial fluid[38]. The lipid content is of particular importance to oil-infused polyethylene as the carbonyl group of lipids could facilitate the diffusion of Lipiodol out of the polyethylene[37].

The ageing protocol used in the present study has been validated by comparing the density, oxidation and the mechanical properties of the artificially aged components with those sterilised and shelf-aged[13]. Most accelerated ageing methods have been developed to simulate shelf ageing caused by free radicals[39,40]. This is because oxidative degradation is catalysed by the free radicals produced during sterilisation[4,41,42]. Implants are normally sterilised and crosslinked using gamma irradiation. The material used in this study was un-irradiated and had not been treated with gamma irradiation. A study by Kurtz *et al.* suggested that any alteration in the manufacturing process (e.g. crosslinking) is likely to alter the oxidation mechanism[31]. Future work will evaluate the concentration of free radicals in the polyethylene prior to ageing in order to better understand the oxidation rate[43].

A limitation of this study, and the standard ageing protocols, was the lack of mechanical loading during ageing. The mechanical loading which will occur *in vivo* can itself can lead to chain scission and accelerate the oxidation via the formation of free radicals, which is the rate controlling step for oxidation[9,44]. The lack of mechanical loading can also affect the leaching results as it may alter the diffusion pathway via alteration of the crystalline arrangement[45]. Future studies should evaluate the effect of static and dynamic loading on the long-term properties of polyethylene.

Conclusion

This study examined the effect of oily fluids on the long–term properties and durability of polyethylene. The results confirmed that the presence of an oily fluid (Lipiodol and Vitamin E) in polyethylene improved the oxidative stability, tensile strength, yield, elongation at failure after ageing, when compared with Untreated and Thermally treated polyethylene. The improved chemical stability is favourable for long-term medical applications; however, the surface radiopacity of the Radiopaque samples reduced by 54% after 4 weeks of accelerated ageing. Although the Radiopaque polyethylene was still clearly visible on a CT scan (500 HU), the surface X-ray attenuation may not be adequate to monitor the clinical performance of a polyethylene joint replacement component through hard tissues over a long period of time (e.g for monitoring wear, creep or migration). It may be possible to mitigate the reduction in radiopacity after ageing through crosslinking, which has proven successful for Vitamin E polyethylene. In summary, oil treated polyethylene has shown a higher tensile and oxidative stability for joint replacement applications compared to standard polyethylene. This work has also highlighted a need for more sophisticated accelerated ageing standard tests, which are more representative of the impact of surrounding physiological fluids, mechanical loading, and the impact of oily additives within polyethylene.

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6.2 Summary

This chapter examined the longevity of radiopaque polyethylene through an accelerated ageing study. It is paramount to investigate the oxidation behaviour of polyethylene because history has shown that the clinical performance of polyethylene joint replacement components is highly influenced by its oxidative stability. Due to the lack of clinical and experimental data on longevity of oil incorporated un-irradiated polyethylene, vitamin E polyethylene (with over 15 years of clinical history) was used as a control. The key findings from the study are summarised below.

- After 4 weeks of thermally accelerated ageing the surface radiopacity of the radiopaque polyethylene was decreased by 54%; however the samples still showed a higher surface opacity than untreated samples (500 HU). The ageing protocol used in this study replicated 5 years of natural ageing, but the accelerated ageing protocol was not validated on oil–infused polyethylene and may not represent the *in vivo* behaviour of the material. As stated in Chapter 1, one of the benefits of a radiopaque polyethylene is that it can be used for post–market device surveillance. Clinical trials will often last five years or more, so the reduction in radiopacity seen in the ageing study may impact on the viability of the material for long–term follow up. However, as explained in the paper, this reduction in the radiopacity may be mitigated by cross-linking which should be investigated as part of future work.

- One of the most promising observations of this study was the high oxidative stability of the samples. Many polyethylene implants have been recalled or removed from the market due to their poor oxidative stability. The results of this study clearly showed that after accelerated ageing the oxidation index of oil-free samples was significantly higher than the oil-infused polyethylene.

- After the accelerated ageing, all the examined tensile properties of the samples treated with Lipiodol were significantly higher than oil-free control samples and were statistically comparable with vitamin E infused polyethylene samples. The retained tensile properties after ageing are indicative that the polyethylene would have a good long–term clinical performance.

- The last part of the study quantified the leaching of Lipiodol and compared it with vitamin E. The majority of leaching out of the oil occurred within the first 2 weeks for both the Lipiodol and vitamin E treated samples, and thereafter the system reached equilibrium and was stable. There is potential for the initial leaching to reduced by cross-linking, or potentially a very short homogenisation step could be introduced to move the Lipiodol away from the surface.

Chapter 7

Conclusions and further work

This chapter summarises the findings reported in this thesis and provides a discussion of the importance and novelty of key points with regards to the objectives set out in Chapter 2.

7.1 Conclusions

Innovative orthopaedic replacements are now required in order to meet the demands placed on them by younger and more active patients; however, there are many cases mentioned in this thesis of new orthopaedic devices that have failed catastrophically and have been withdrawn from the market. The clinical longevity of orthopaedic prostheses is measured in decades and early failure may not become apparent until several years after implantation. To avoid any adverse outcomes, organisations such as the Orthopaedic Data Evaluation Panel (ODEP) have been set up to ensure new devices are rigorously checked for safety as well and demonstrate improvements in patient outcomes prior to clinical widespread use. In the case of polyethylene it is rare that a new polyethylene is brought to the market, in part because UHMWPE bearing surfaces perform well in general. However, there is scope for additional functionality, such as radiopacity, antioxidants or perhaps antimicrobials, which could address issues which are currently seen clinically. The incorporation of oil-based additives into polyethylene, such as Lipiodol which is explored in this thesis, may be provide additional functionality but it is paramount that the material causes a demonstrable clinical improvement in outcomes.

7.1.1 Medical imaging using X-ray based methods

Performing clinical post-market surveillance is crucial in order to understand the behaviour of a new product design; and the gold standard method for accomplishing this is MBRSA due to its high accuracy. The sub-millimetre accuracy of MBRSA analysis means a sufficient clinical data can be collected in a relatively short time using a small group of patients. Currently, it is not possible to use MBRSA analysis for all-polyethylene implants due to the material's poor X-ray visibility. It is also not possible for a surgeon to use fluoroscopic methods to assist

with placement of an all-polyethylene component (e.g. for maxillofacial applications), and case studies demonstrate clinical difficulties diagnosing mobile bearing dislocation or fracture. In this thesis a radiopaque polyethylene was created through the diffusion of an iodised oil-based contrast agent; the resultant radiopacity was quantified using CT and then its visibility within clinical X-ray imaging was assessed, and finally the feasibility of performing MBRSA was examined.

- The surface radiopacity of polyethylene was significantly enhanced through the diffusion of Lipiodol. The surface radiopacity of samples after treatment was over 500 HU and the samples were clearly visible on CT scan images. Samples were subjected to 4 weeks of accelerated ageing (equivalent to 5 years of implantation), which caused the surface radiopacity to reduce significantly from its original value (54% decrease on average), but were still clearly visible on the CT scan images. However, for joint replacement applications when the surrounding bone and soft tissue is considered, this reduction in radiopacity may impair the visibility of the component. The lower attenuation of polyethylene after several years *in vivo* could also reduce the precision of the MBRSA measurements lowering the quality of follow-up data. However, the literature on vitamin E infused polyethylene indicates that cross-linking could provide stability to the polymer, and may mitigate the reduction in radiopacity with time. The cross-linking of the amorphous regions has been shown to hinder the pathway of diffusion[189], and so would reduce the mobility of the Lipiodol. Moreover, the accelerated ageing protocol for polyethylene has not been validated for oil-infused polyethylene and it may not be representative of the clinical behaviour of the material.

- The Lipiodol–treated unicompartmental knee bearings were visualised under a clinically representative X-ray set up using both standard and stereo-radiographs. Even after using 30 mm of PMMA to replicate soft tissue, the radiopaque unicompartmental knee bearings could be visualised in the stereo-radiographs. The knee bearings were final components, and so had already undergone cross-linking, in theory this would reduce the diffusion of Lipiodol into the samples, but the results were comparable with the uncrosslinked tensile test samples analysed using CT. There was a noticeably uneven distribution of Lipiodol within the sample, with a greater concentration at the surface, but this would be expected for a diffusion-based process. Aesthetically it may be an issue, because the samples had an oily feel to them at the surface, and this may be not popular among surgeons or patients.

- The radiopaque polyethylene components had sufficient radiopacity to be measured using MBRSA, and the precision of MBRSA measurements was comparable with e metallic implants for translational movements (0.03-0.50 mm). The precision for rotational movements was lower than for metallic implants analysed, and this may be in part a result of the high symmetry of the knee bearings analysed, but also there were issues attaining an accurate CAD model of the components surface. The surface shape changed after treatment due to swelling of the samples, and although attempts were made to create a

laser-scanned CAD model of the component shape after treatment, equipment limitations led to inaccuracies. However, with the correct laser scanning equipment, and potentially for non-symmetric components, it is likely that the precision of rotational movement measurements using MBRSA could be improved.

- Despite the high symmetry of the samples and the low quality of surface model, the MBRSA analysis demonstrated a very high level of accuracy (more 95%) in the superior-inferior direction. As wear typically occurs in the superior-inferior direction, MBRSA could potentially be used for the quantification of linear wear of all-polyethylene implants. Currently, linear wear in an MBRSA study is measured from the metallic implants, which may introduce inaccuracies if events such as microseparation occur which are unseen, furthermore such analyses are not available for all-polyethylene implants.

- In Chapter 4 the visibility of the components and the MBRSA measurement accuracy was also investigated when the polyethylene was next to a metallic part and/or a radiopaque bone cement. Neither the metal or the bone cement impaired the visualisation of the radiopaque bearing and the precision and accuracy of the parts when cemented to a tibial Sawbone were comparable with the un-cemented implants. This demonstrates that the radiopaque bearing could be useful for a variety of implant designs.

7.1.2 Material properties

One potential risk is that the introduction of the oil into the polyethylene will cause a change in the material properties, resulting in failure of the implant due to factors such as creep, wear or fatigue. Consequently, a range of material tests were performed in Chapters 3 and 6 on the radiopaque polyethylene to assess whether it may be at risk of premature material failure under joint loading. At high Lipiodol concentrations a detrimental effect on the material properties was observed, but diffusion at a temperature of 105°C for 18 hours was able to create a high radiopacity while maintaining equivalent material properties to the untreated standard polyethylene. The behaviour of the polyethylene after ageing was also investigated and the Lipiodol-infused polyethylene appeared to be more resistant to material degradation than conventional polyethylene. The key findings from the assessment of the material behaviour of the radiopaque polyethylene are summarised below.

- From a clinical perspective, the degree of crystallinity is one of the most critical properties of polyethylene. Historically significant changes to the crystallinity of polyethylene, when either increased or decreased, can lead to a poor outcome. Hylamer polyethylene, with 70% of crystallinity, was created in order to enhance the oxidative resistance of polyethylene; however, the high degree of crystallinity reduced the ductility and long-term wear resistance of the material, and more than 84% of Hylamer bearings failed catastrophically within the first 4 years. The results of this study confirmed that the presence of Lipiodol caused no significant alteration in the crystallinity of polyethylene, and after 4 weeks of ageing the crystallinity of polyethylene was still comparable with untreated polyethylene.

- The oxidative stability of polyethylene is another clinically important property. Oxidised polyethylene has a poor wear resistance which creates wear particles that cause further clinical complications as they can trigger inflammatory responses, it is also more prone to material fracture and surface damage such as pitting and delamination. The oxidative stability of the radiopaque polyethylene was thoroughly investigated through an accelerated ageing study. Prior to ageing it appeared that the Lipiodol-infused polyethylene was oxidised but this was an artefact resulting from the data analysis. Lipiodol has an ester peak in the FTIR spectra which overlaps the oxidation product's aldehyde peak and so when oxidation is quantified according to the ASTM standard the oxidation index is artificially high. However, after 4 weeks of ageing the oxidation index of the radiopaque polyethylene remained almost constant when the Untreated and Thermally treated controls had a large increase in oxidation index. From this it can be inferred that the radiopaque samples had a high oxidative stability; it is possible that the ester peak obscures the oxidation peak both before and after ageing but there were no other peaks in the FTIR spectra which would represent oxidation by-products (e.g. ketone and trans-vinyl). To be absolutely sure of the oxidative stability of the material, further studies should examine the oxidative stability of radiopaque polyethylene under more realistic physiological conditions such as in the presence of synovial fluids while under applied load.

- The tensile properties of polyethylene give clues as to what will be the long term clinical performance of the material; a reduction in the tensile modulus tends to be associated with poor creep properties and wear resistance, while an increase in the modulus can be associated with reduced fatigue resistance. The results of this study demonstrated that samples treated at 105°C for 18 hours had no significant change in their tensile properties as compared to untreated polyethylene. However, a plasticising effect on the polyethylene due to the Lipiodol was recorded in this study, where the elongation at break increased after treatment, which may adversely affect the creep properties of the material. The potential to control the distribution of Lipiodol through the sample may enable some mitigation of this effect, whereby if the Lipiodol is restricted to the surface of the implant the bulk material properties would retained. The results of this study also showed that after 4 week of accelerated ageing, the modulus of radiopaque samples reduced by at least 55%; this large reduction reflects the severity of the test, and when compared to the untreated samples where the modulus reduced by 84% it can be concluded that the Lipiodol has some protective effect on the degradation of the polyethylene. Lipiodol is a mixture of hydrocarbons, but it contains a large amount of α-tocopherol (vitamin E), and so it may be that the contrast agent is providing an anti-oxidant effect.

7.1.3 Manufacturing barriers

Barriers in terms of scaling up of a manufacturing process can stop a successful component being produced. In the case of Lipiodol-infused polyethylene there are many challenges in its production: (1) the diffusion takes 18 hours to be performed, (2) the diffusion temperature and

time would need to be tailored for each individual component size and geometry, and (3) the Lipiodol is very costly. To assist with these challenges a study was performed to see whether the diffusion could be modelled using numerical methods, to enable more efficient planning of treatment of the polyethylene components. A finite element-based Fickian diffusion model was developed for more accurate prediction of optimal parameters in the manufacturing process; namely time and temperature.

- A Fickian diffusion model was able to represent the diffusion profile to a reasonable accuracy (to within 20% of the true value) but only if the model were in 3-dimensions. This adds complexity to the analysis process and in terms of manufacturing planning would require a skilled engineer to perform the analysis for each component. Nevertheless, the tool would still save time because the only other option is trial and error.

- If a more accurate model were required for manufacturing purposes there are several improvements which could be made. The model was most accurate at lower treatment temperatures; and this may be because in the experiments the temperature is not only influencing the diffusion but also the structure of the polyethylene (e.g. its crystallinity). On this basis the accuracy of the model may be improved through the incorporation of these structural changes in the polyethylene properties.

- A key barrier to the implementation of this technology is the cost of the contrast agent. At the time of writing, 10 ml of Lipiodol costs approximately 2000 and so if the radiopaque polyethylene were to become commercially viable an alternative contrast agent would need to be developed. One possibility is that vitamin E could be iodised, which would mean the material would more closely represent vitamin E polyethylene. Lipiodol is made from poppyseed oil which is a more expensive oil to produce; studies have shown that oil-based contrast agents can be made from peanut oil in a more cost-efficient way, and so that may provide an alternative option. Other possibilities are suggested in the Future work section below.

7.1.4 Leaching of Lipiodol

It is possible for Lipiodol to diffuse out the polyethylene samples thereby causing the radiopaque polyethylene to lose its functionality and it was very important to investigate this. In Chapter 6 the leaching behaviour of Lipiodol was investigated under simulated physiological conditions, and measured from gravimetric changes over 8 weeks. The leaching rate was compared with vitamin E polyethylene as the only other oil-infused polyethylene which is currently used.

- After 8 weeks the radiopaque polyethylene was still identifiable in CT scan images, even though leaching of approximately 20% of the original quantity of Lipiodol occurred. It is possible that the leaching of Lipiodol can be mitigated through crosslinking, which has been shown to reduce leaching of vitamin E.

- As leaching of the Lipiodol has been confirmed to occur, it is really important to check the safety of the oil within the body. Lipiodol is a contrast agent which has approval for clinical use, and it typically used to visualise tubular structures in the body such as the lungs and the Fallopian tubes. It is injected into these areas in larger quantities than as would diffuse out from the polyethylene; however, clinically Lipiodol would never be injected into the synovial fluid, and so it is unknown whether the contrast agent would cause any adverse responses within the joint and these tests have yet to be performed.

In summary, the three key contributions of this study are: firstly, it is possible to enhance the radiopacity of polyethylene using Lipiodol to develop a material suitable for long–term medical applications. Secondly, the radiopaqueness can be predicted based on the parameters using the model presented in this study. The application of this model is not limited to the medical industry and can be used to predict the oil concentration in any type of polyethylene material. Finally, this study proved that the presence of oily fluid containing tocopherols (vitamin E and Lipiodol) will improve the chemical and mechanical stability of polyethylene.

7.2 Future work

The main bulk of work in this thesis relates to the effect of Lipiodol on the critical material properties of polyethylene for long term medical applications. In Chapter 1, Table 1-1 details the different standard tests required, and not all of them have been performed in this thesis, and several questions remain unanswered. Further testing to be prioritised should include; the fracture toughness, the wear resistance, fatigue resistance, creep resistance, swell ratio tests, small punch tests, and Izod impact tests.

Lipiodol, is not the only available oil-based contrast agent, and its high expense and the fact that it contains different lengths of fatty acids could deter its use commercially. Domenick *et al*, invented a way to produce halogenated fatty acids, and in a similar manner, this work first attempted to create iodinated Lenolenic acids; this was not reported in the main thesis work as a different avenue was explored but it is attached in Appendix B. Attaching three iodine groups to the Lenolenic acid is thermodynamically complex, and this was the main difficulty encountered in this approach. Future work may accomplish the creation of iodinated Lenolenic acids that will replace Lipiodol; alternatively there are already other more cost-efficient iodinated oil-based fluids with shorter fatty acid chains, but these have limited commercial availability at the time of writing[51,52].

An additional area of research related to the work contained in this thesis is the biocompatibility of radiopaque polyethylene. The alteration in the surface of polyethylene can lead to a greater propensity for the material to form biofilms[59], and so these tests would need to be performed. Furthermore, it is possible that there are adverse biological responses caused by the Lipiodol. The leaching rate of Lipiodol out of the polyethylene measured in this work was very

slow (less than 0.002 $\pm$0.007 g/day), but an excess amount of iodine can cause acute or chronic inflammatory disease such as thyroiditis and sialadenitis [52]. It is important to examine the compatibility of the radiopaque polyethylene and future work should thoroughly understand and examine the safety of the radiopaque polyethylene for orthopaedic applications.

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Appendix A: Tensile properties of samples treated with Lipiodol at 125 ° C

The aim of this section is to provide some background information on the feasibility stage of the second paper (Characterisation of the physical, chemical and mechanical properties of a radiopaque polyethylene). This section explains the results of the feasibility stage and further information with regards to the methodology is included in the paper.

The results of this staged showed that at 125 ° C, Lipiodol can have decremental effect on some of the tensile properties of polyethylene (72%. decreased in the young modulus (Figure -1), no statistically significant change in UTS and yield). One of the main objective of this stage of to ensure the treatment condition does not cause any significant alteration in the critical properties of polyethylene In addition the oxidation Index of the samples treated at 125 125 ° C was as high as 4. This high oxidation index can be associated with the high concentration of Lipiodol, according to ASTM F2120, the sample's oxidation index should be less than 1 for clinical use, hence pursuing with that temperature would have not add any additional benifits to the overall aim of the study.

Figures below summarise the main results of the study.

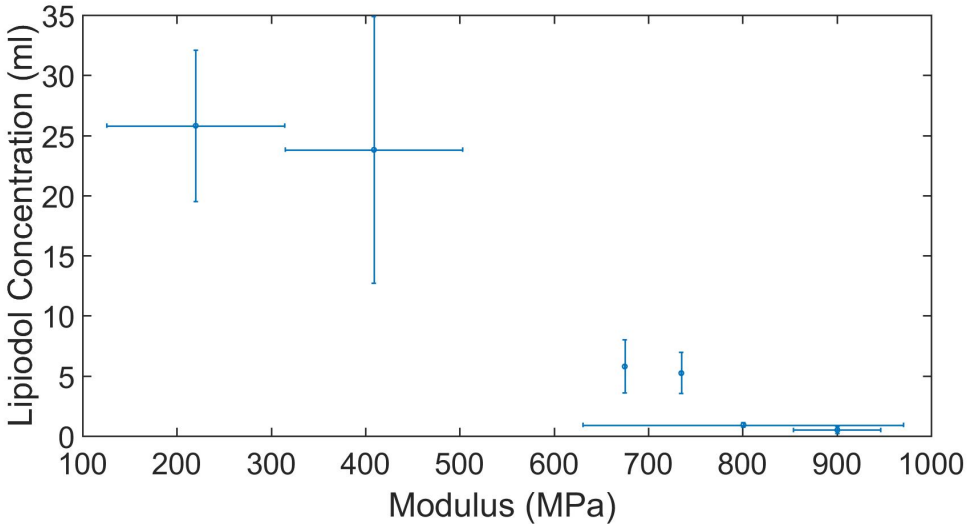

Figure -1: The modulus of the polymer reduced as the concentration of the Lipiodol increased (R=-0.9). The concentration was calculated from the calibration curve.

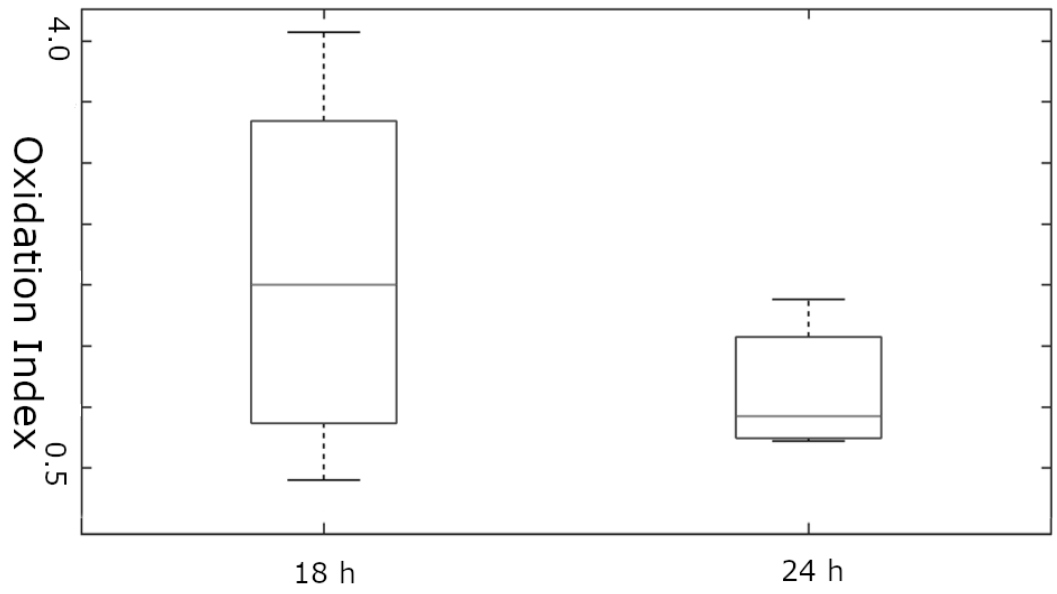

Figure -2: Oxidation peak was detected for samples treated at 125^0C for 18 and 24 hours using FTIR. The difference between two groups is not statistically significant (p=0.6)

Appendix B: NMR analysis of aged Lipiodol

Poppy seed oil (the precursor for lipiodol) is a triglyceride, with typically 60-70% linoeleic side chains (these have two carbon-carbon double bonds). The process that makes lipiodol removes the unsaturation (double bonds) using iodine. Heating lipiodol will result in some of the chains losing iodine again and regenerating double bonds. The signal for the double bonds can be seen around 5.25 to 5.40 ppm in the 1H NMR spectra. All triglyceride side chains end with a methyl, the signal for which can be seen around 0.8 to 0.95 ppm, and equates to 9 protons. Thus the ratio between this signal and the signal for the double bond protons can give an indication of how much unsaturation is present.

Sample	Integral (5.25-5.40 ppm)	Iodine number (unsaturation)
Lipiodol	0.269	0.13
85 deg 24 h	0.623	0.31
95 deg 24 h	0.572	0.28
105 deg 24 h shelf aged	0.169	0.08
115 deg q8 h	1.251	0.62
115 deg 24 h	1.558	0.78

Appendix C: Halogenation of Linolenic acid

iodised poppy seed oil

15/12/2016 16:34:55

Acquisition Time (sec)	2.0447	***Date***	Dec 14 2016	***Date Stamp***	Dec 14 2016		
File Name	C:\Users\atj04\Documents\NMR\iodised_poppy_seed_oil_20161214_01\PROTON_01.fid\fid					***Frequency (MHz)***	500.06
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	16384	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	14.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	3000.3088	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8012.82	***Temperature (degree C)***	25.000